PRESBYTERIAN-ST. LUKE'S HOSPITAL

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Asymmetrical Fusional Vergence

Book Review

Abstracts and Reviews

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FOUR YEARS EXPERIENCE WITH IMPLANTED CARDIAC PACEMAKERS*

Richard A. Carleton, M.D.[1]
Robert W. Sessions[2]
Milton Weinberg, M.D.[3]
James A. Hunter, M.D.[4]

The observations of Hyman[1] in 1932 demonstrated the feasibility of stimulating hearts to beat at a normal rate after hypoxic arrest. Weirich and his co-workers in 1957[2] first applied an external pacemaker to man using wires attached to the epicardium. Chardack *et al*,[3] in 1960, were the first totally to implant an electronic pacemaker. The clinical experience at Presbyterian-St. Luke's Hospital began in May, 1961; results in the first 10 patients have been reported previously.[4] The present report describes the results in the succeeding 60 patients who have been treated with permanently implanted electronic cardiac pacemakers.

DESCRIPTION OF PATIENTS*

The 60 patients ranged in age from 5 to 83 years; 43 patients were between the ages of 60 and 79. Thirty-six were male. Seven patients had evidence of ischemic heart disease manifested as angina pectoris or as one or more myocardial infarctions. In two patients complete artioventricular (A-V) block occurred at the time of cardiac surgery for a ventricular septal defect. One patient had coexistent complete A-V block and severe calcific aortic stenosis. Seven patients, all under the age of 60, had a myocardiopathy of unknown cause. Three patients required pacemakers because of paroxysmal atrial arrhythmias which alternated with sinus nodal arrest sufficient to produce Stokes-Adams episodes. Forty patients, all over

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*We are indebted to many people, including John S. Graettinger, M.D., Ormand C. Julian, M.D., Marvin S. Rosenberg, M.D., Hushang Javid, M.D., Joseph J. Muenster, M.D., William S. Dye, M.D., and H. Gunther Bucheleres, M.D., who have contributed their clinical and surgical skill to these patients.

the age of 50, had complete A-V block without identifiable cause; these individuals were presumed to have degeneration of the cardiac fibrous "skeleton" as described by Lev.[5]

The reasons for pacemaker implantation were two. Two patients had intractable congestive heart failure as an accompaniment of their slow idioventricular rhythm. Forty-six patients had experienced Stokes-Adams episodes due either to abrupt slowing of an idioventricular focus or to periods of rapid ventricular tachycardia. Both congestive failure and Stokes-Adams episodes occurred in the other 12 patients.

DESCRIPTION OF PACEMAKERS

The pacemakers used in this series of patients have been made at Presbyterian-St. Luke's Hospital by one of us (RWS). The basic circuit diagram has been published elsewhere.[6] Briefly, mercury batteries supply electrical power to an oscillating circuit which permits discharge of a capacitor across the myocardium at a rate of approximately 75 per minute. Each impulse has a duration of 2 msec. and delivers approximately 10 mamp. at 6.0 volts. The electronic components and batteries are embedded in an epoxy resin which is then coated with silicone rubber.

The wires used to connect the pulse generator to the myocardial electrodes have a synthetic fiber core. Around this, four ribbons of stainless steel are wound in a helical spiral. These are soldered to platinum electrodes. The wire is enclosed in a polyethylene sheath; in turn this is enclosed in a silicone rubber tubing which is sealed to epoxy at each end.

The impulses are delivered to the myocardium by either of two types of electrodes. Fifty patients have had a left thoracotomy and pericardiotomy. For this approach, the wires terminate at epoxy covered platinum disks 9 mm in diameter. These disk electrodes are sewn to the epicardium near the apex of the left ventricle. For ten patients one wire has terminated as a platinum cylinder 6 mm in length and 3 mm in diameter. This has been inserted, under local anesthesia, either in an external jugular vein or in a cephalic vein at the shoulder. The electrodes have been advanced under fluoroscopic control into the apical segment of the right ventricular cavity to ensure good endocardial contact. With this system, the other wire terminates in a disk electrode implanted subcutaneously. The pulse generator is placed in a pocket fashioned in subcutaneous tissue overlying one pectoralis muscle with either mode of myocardial stimulation.

Replacement of pulse generator units is performed under local anesthesia. The generator is exposed through a 10 cm incision, the wires are cut, and a new generator is spliced to the existing wires leading to the heart. The splices are performed with crimped connectors with a stainless steel conducting core. The splices are sealed in silicone rubber prior to implantation of the new generator.

RESULTS

Patient Survival

Table 1 shows the status of this series of 60 patients at intervals after initial pacemaker implantation. There have been three deaths during hospitalization for implantation of an epicardial unit; one of these occurred from a coronary arterial embolus on the day after both an aortic Starr-Edwards prosthesis and a pacemaker had been implanted. One patient died of severe cor pulmonale six days after unsuccessful efforts to implant an endocardial unit. One other patient died suddenly at home two weeks after insertion of an endocardial unit. Thus, the mortality within the first month

Table 1. Summary of Patients with Implanted Pacemakers
Follow-up Period

Type of Pacemaker	1 mo.			6 mo.			1 yr.			2 yr.			3 yr.			4 yr.		
	Dead	Alive	Pacing	Dead	Alive	Pacing	Dead	Alive	Pacing	Dead	Alive	Pacing	Dead	Alive	Pacing	Dead	Alive	Pacing
Epicardial	3	47	47	2	40	39	2	31	30	1	17	17	2	4	4	1	1	1
Endocardial	2	8	8	0	6	5	0	3	3									
TOTALS	5	55	55	2	46	44	2	34	33	1	17	17	2	4	4	1	1	1
Cumulative Deaths	5			7			9			10			12			13		
Cumulative Mortality	8.3%			13.2%			20.9%											

after surgery has been 8.3%. Two additional deaths have occurred between the first and seventh months after surgery. Forty-six were alive six months after surgery; two of these were no longer being paced, but each had fortuitously reverted to normal A-V conduction. Thirty-four patients have been followed for more than one year. Two deaths have occurred between six months and one year, yielding a cumulative survival rate of 79.1% during the first year of follow-up. Seventeen patients have been followed for two years and four patients for three years.

Division of patients by the period of implantation provides figures for survival comparable to the type of analysis conducted by others.[3] Of the 24 patients who had pacemakers implanted between one and two years ago (11/1/64 to 10/31/65), 19 (20.8%) have survived. Of six patients whose units were inserted between two and three years ago, five are surviving (16.7%).

Pacemaker Unit Fate

Replacement of the pulse generator unit has become a routine procedure; no complications have occurred to the present time. No patient has undergone a second thoracotomy for replacement of a defective unit. Two patients have had either a broken wire or an abnormally high myocardial stimulation threshold, 32 and 39 months after the initial implantation respectively, and have had an endocardial unit inserted to avoid a second thoracotomy.

Forty-three instances of pacemaker failure have occurred; each has been replaced. Thus, 113 pacemaker units have been used. The reasons for pacemaker failure can be considered in three categories. The first is failure of an individual electronic component. The transformer in the oscillating circuit has failed on two occasions, six and nine months after implantation respectively. Two capacitors have changed their capacitance value sufficiently to modify the pacemaker rate four and six months after implantation. This represents a 3.5% incidence of component failure. Wire or electrode failure, or myocardial threshold elevation comprise the second category. Two failures in this category have been mentioned previously. One additional failure has occurred at 14 months, necessitating the use of a subcutaneous indifferent electrode. Two of the splices made at the time of replacement have been improperly sealed with silicone rubber and have failed four and eight months respectively after implantation. This represents a 4.4% incidence of failure in this category. The third category is comprised of inevitable failures—that of the mercury battery power supply. Thirty-four units have required replacement because of battery failure. This has occurred between nine and 31 months (average 16 months) after implantation. Seven of these battery

failures have occurred prior to 15 months and are considered to be instances of premature failure. This period of battery function which is shorter than that expected from "shelf life" studies of these batteries, is largely related to slight but harmful imbibition of water by the epoxy seal. Improved epoxies are currently under study.

The failure rate from all causes in the first twelve months has been 9 of 113 units (8%).

COMMENTS

The paroxysmal hazards of acquired complete atrioventricular block have caused a high mortality rate in patients treated by drugs alone.[7,8] The survival rates in the present series and in that of Chardack and his co-workers[3] has been consistently higher.

The patient with acquired complete A-V block requires prompt therapy when Stokes-Adams episodes are occurring. At present, this therapy is best undertaken in four sequential stages. Firstly, isoproterenol given intravenously at a rate of 4 to 8 mcg. per minute will usually accelerate a slow idioventricular rhythm sufficiently to permit careful completion of the second stage. Then a temporary transvenous electrode catheter can be inserted and connected to a battery powered external pacemaker. With this in place in the right ventricle, the patient can safely undergo study and therapy of coexistent problems to insure optimal condition for permanent pacemaker implantation.

The greater simplicity and lower operative risk of the permanent transvenous approach will probably lead to increasing use as experience indicating reliability of this approach increases.

SUMMARY

Sixty patients have been treated by pacemaker implantation at Presbyterian-St. Luke's Hospital between August, 1962 and October, 1966. The cumulative mortality figures have been 13.2%, 20%, 37%, and 75% at six months, one year, two years, and three years respectively after surgery. Nine pacemakers have required replacement after less than one year because of failure of electronic components, electrodes or wires, or premature battery depletion.

Implanted pacemakers provide an important therapeutic tool for the prevention of the sequelae of complete atrioventricular block. □

REFERENCES

1. Hyman, A. S.: Resuscitation of the Stopped Heart by Intracardial Therapy. II. Experimental Use of an Artificial Pacemaker. *Arch. Intern. Med.*, 50:283, 1932.
2. Weirich, W. L.; Paneth, M.; Gott, V. L.; and Lillehi, C. W.: Control of Complete Heart Block by Use of an Artificial Pacemaker and a Myocardial Electrode. *Circ. Res.*, 6:410, 1958.
3. Chardack, W. M.; Gage, A. A.; Federico, A. J.; Schimert, G.; and Greatbatch, W.: Five Years' Clinical Experience with an Implantable Pacemaker: An Appraisal. *Surgery*, 58:915, 1965.
4. Andersen, J. G.; Behravesh, M.; Sessions, R.; Heckel, E.; Weinberg, M.; and Fell, E. H.: The Treatment of Complete Heart Block with Electronic Pacemakers. *Pres.-St. Luke's Hosp. Med. Bull.*, 1:2, 59, 1962.
5. Lev, M.: The Normal Anatomy of the Conduction System in Man and its Pathology in Atrioventricular Block. *Ann. N.Y. Acad. Sci.*, 111:817, 1964.
6. Carleton, R. A.; Sessions, R. W.; and Graettinger, J. S.: Dual-rate Pacemaker. *J. Thorac. Cardiov. Surg.*, 48:684, 1964.
7. Curd, G. W., Jr.; Dennis, E. W.; Jordan, J.; McNamara, D.; Montero, A. C.; Peterson, P. K.; Pruitt, R. D.; and Schnur, S.: Etiology of Atrioventricular Heart Block: A Study of its Relevance to Prognosis and Pacemaker Therapy. *Cardiov. Res. Cent. Bull.*, 1:63, 1963.
8. Friedberg, C. K.; Donoso, E.; and Stein, W. G.: Nonsurgical Acquired Heart Block. *Ann. N.Y. Acad. Sci.*, 111:835, 1964. □

INJURIES OF THE MEDIAN NERVE AT THE WRIST

Francis M. Howard, M.D.[1]

INTRODUCTION

Injuries of the median nerve at the wrist are of great importance because this nerve supplies the "eyes" of the fingers (Fig. 1). It is through sensation and through these eyes that the fingers communicate tactile knowledge to the brain. Sensation is necessary to tie one's shoes with dexterity, to button a coat, to distinguish velvet from silk, or to find a light switch in the dark. It is *perceptive sensation* that enables the fingers to feel what they are holding, how they are holding it, and how strongly they are holding it. With an injury to the median nerve, this precise sensation may be lost, leaving only protective sensation. Recovery of sensation after injury to the median nerve may mean only a return of protective sensation—a type of sensation that is primitive and only protects against a burn or a similar injury (Fig. 2).

Many tests for sensation have been devised by neurologists who were chiefly interested in a synthesis of the individual neurological modalities in order to achieve a diagnosis. Generally, they were not so concerned with perceptive sensation or tactile gnosis per se.

It is the purpose of this paper to examine median nerve injuries at wrist level and to analyze them as to location, age of the patient, technical difficulties of repair, and complexities accompanying the repair when other structures are also injured.

EXAMINATION AND DIAGNOSIS

When a patient enters the emergency room with a bleeding laceration of the wrist, the wound should be inspected for arterial bleeding and tendon injuries. The wound should be covered with a sterile dressing and no aggressive probing or contamination of the wound permitted. Sensation should be tested by pin prick, but the common mistake of asking the patient whether he feels the pin prick when he actually sees the pin should be avoided by a blindfold over the patient's eyes. The diagnosis of median nerve

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Fig. 1.—The median nerve—the "eye" of the fingers.

laceration will generally not be established by motor loss, but usually by loss of sensation. Whenever a laceration of the palmaris longus tendon is seen in the wound, it is mandatory that the median nerve be explored for an injury. It is common that the examiner recognizes the laceration of the palmaris longus tendon and proceeds to an anatomical repair of this tendon but misses the divided median nerve hiding below (Fig. 4).

To achieve an accurate and objective assessment of sensation of median nerve function, four tests are valuable:

1. **The Ninhydrin Print Test:** This test is predicated on the principle that a patient with normal sensation sweats, but when a sensory nerve is severed, no sweat is discernible. Therefore, it is an objective test and records on paper the results of a loss in sensation. This makes it especially valuable in medical-legal and compensation cases. It can be utilized when the patient is unconscious, intoxicated, or too young to be cooperative. This test requires only that ninhydrin solution be sprayed onto the paper on which the patient's fingerprints have been taken and that the paper then be heated (Fig. 5).

2. **The Coin Test:** The physician keeps the dorsum of the patient's finger flat against the examining table and questions him as to whether the coin which is stroked against the finger has a rough (quarter) or a smooth (nickel) edge. Proprioception and pressure sensation can be eliminated by preventing the patient from pushing his finger against the coin. This test is readily available and can be performed quickly at the patient's bedside or in the examining room.

3. **The Weber Two-Point Discrimination Test:** This is a helpful and accurate test for sensation and, when properly administered, gives a great amount of information. The purpose of the test is to determine how close the two points on a caliper can be brought together before the patient will feel only one point. Normally, he should be able to feel the two points of a caliper on any span greater than 2 to 4 mm. when touched against the palmar surface of the fingertip. In lacerations of a sensory nerve, this span is often 30 mm. or greater.

4. **The Moberg Pickup Test:** This is a test of the patient in action and tells how the patient actually uses his sensation. The patient is asked to pick up several small objects and place them in a container, first with the right hand and then the left hand. He is then blindfolded and asked to repeat the procedure with speed. It will be noted that the hand lacking in sensation will grope about and fumble over the container. The hand where the median nerve is injured will turn to its ulnar side when seeking the objects, since it is a fundamental principle of the hand that "function follows sensation."

The physician can palpate the rough grooves and whorls in the normal finger tip and distinguish them from the smooth, slippery surface present in a finger without sensation. It may take the examiner some time to develop this facility, but it is a rapid and reliable guide to the examination of the hand.

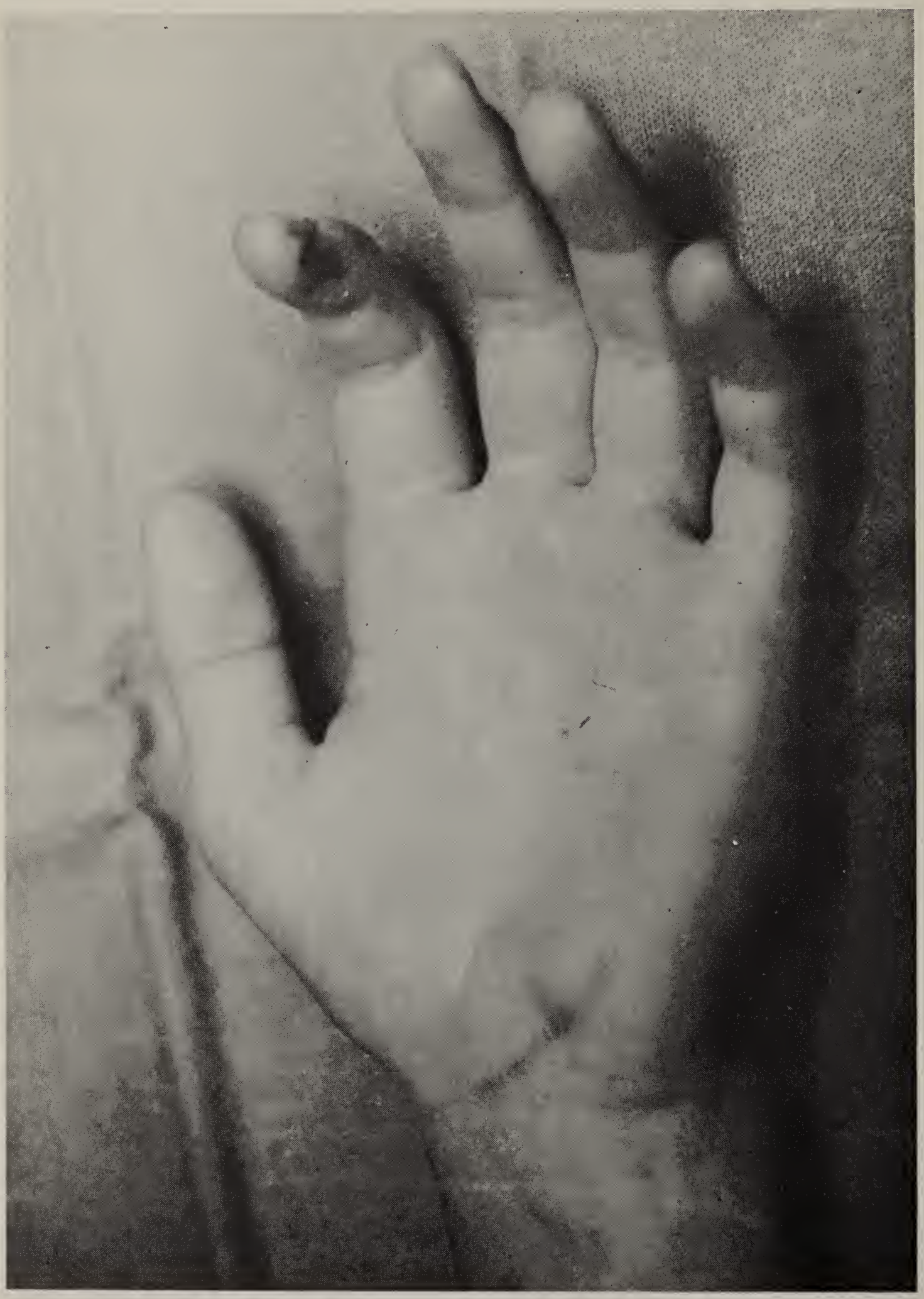

Fig. 2.—Ulceration of index finger from burn after median nerve laceration.

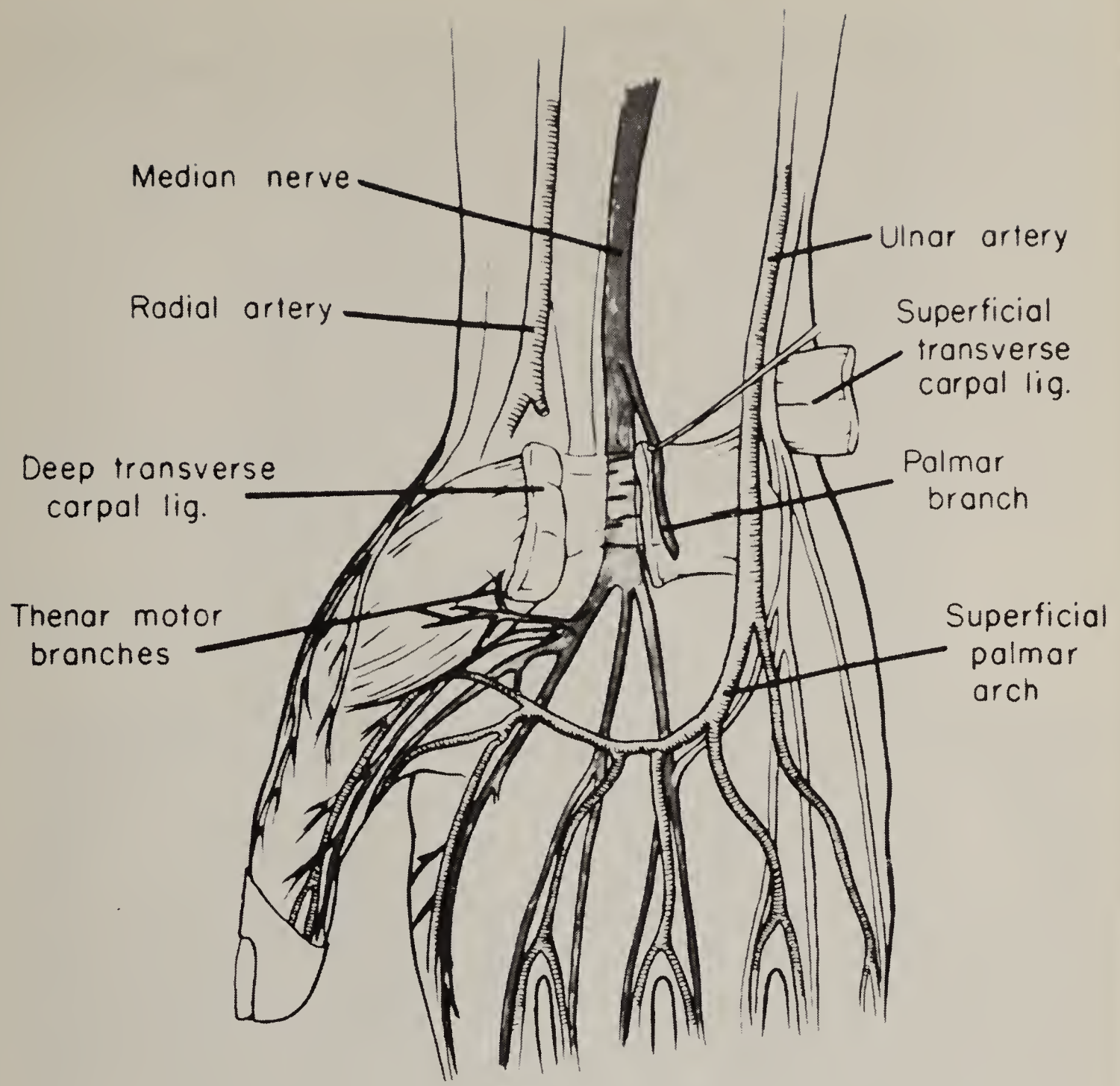

Fig. 3.—Anatomy of the median nerve at the wrist.

Carpal Tunnel Syndrome

An occasional consequence of median nerve injury at the wrist is the *carpal tunnel syndrome*, an entity characterized by entrapment of the median nerve by the overlying volar carpal ligament, surrounding synovium, or scar tissue. It results initially in loss of sensation in the lateral three and a half fingers, followed later by motor loss in the thenar muscles.

Tanzer has pointed out that forced flexion of the patient's wrist against the examining table can often reproduce the symptoms, as this will squeeze the median nerve against the carpal ligament anteriorly and the flexor tendons posteriorly.[3]

Electromyographic evaluation and nerve conduction studies are of considerable value in establishing the diagnosis of carpal tunnel syndrome. A delay in the wrist latency time of 5 msec. or more is of significance[4] (Fig. 6).

Simple section of the constricting volar carpal ligament may suffice, but it may be necessary to perform neurolysis or synovectomy.

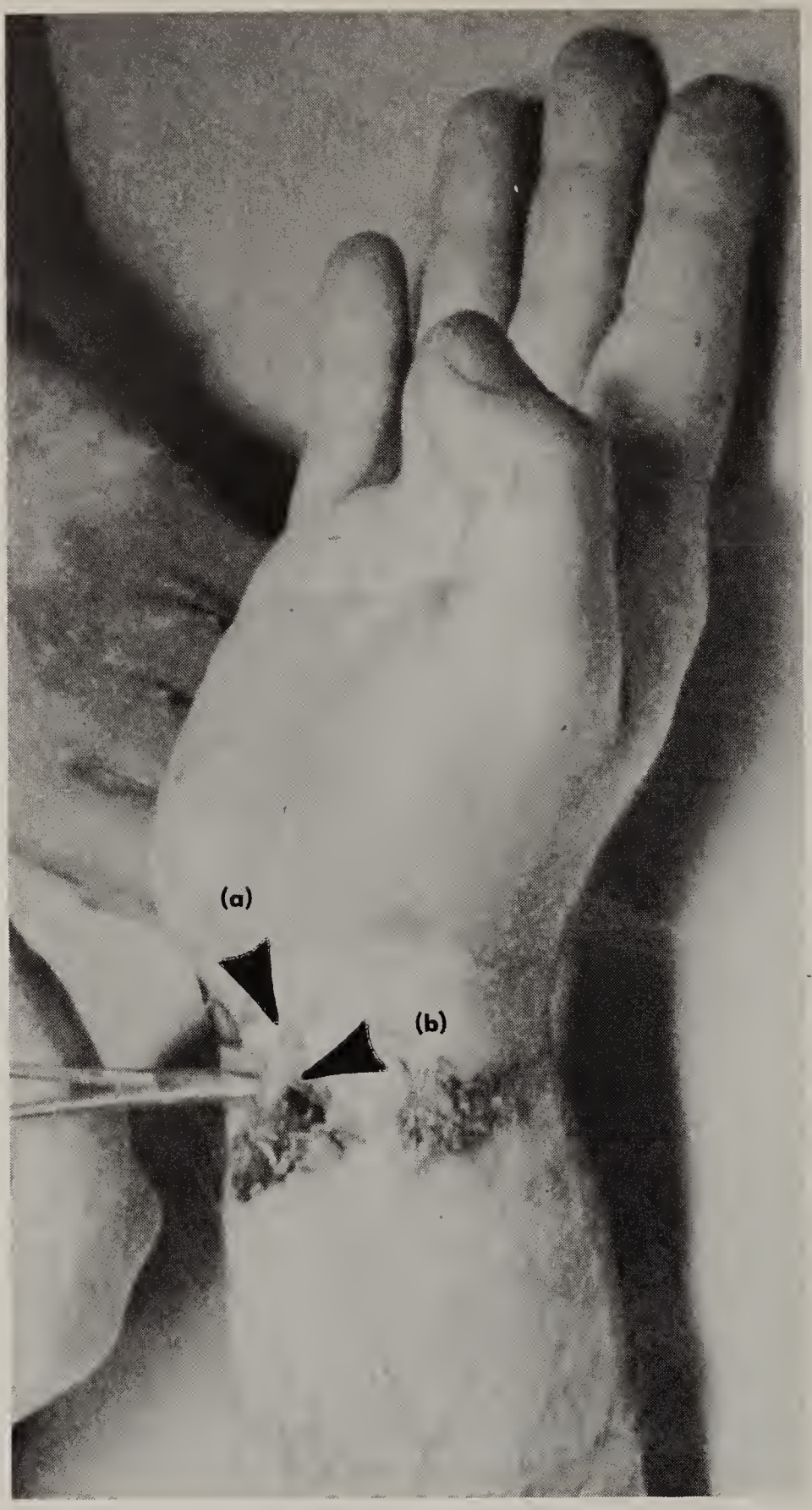

Fig. 4.—Median nerve laceration at the wrist with division of palmaris longus tendon (a) lying superficial to nerve (b).

TREATMENT

Orientation of Nerve Fibers

In a laceration of a nerve at the wrist level, meticulous orientation of the nerve ends is of great importance. At this level the motor fibers of the median nerve lie chiefly on the ventral surface, but the reverse arrangement holds for the ulnar nerve[2] (Fig. 7). Therefore, a partial laceration of the median nerve generally results in motor loss. In the region of the lumbrical muscles, the nerves are chiefly of the pure type and orientation is not so important in the repair.

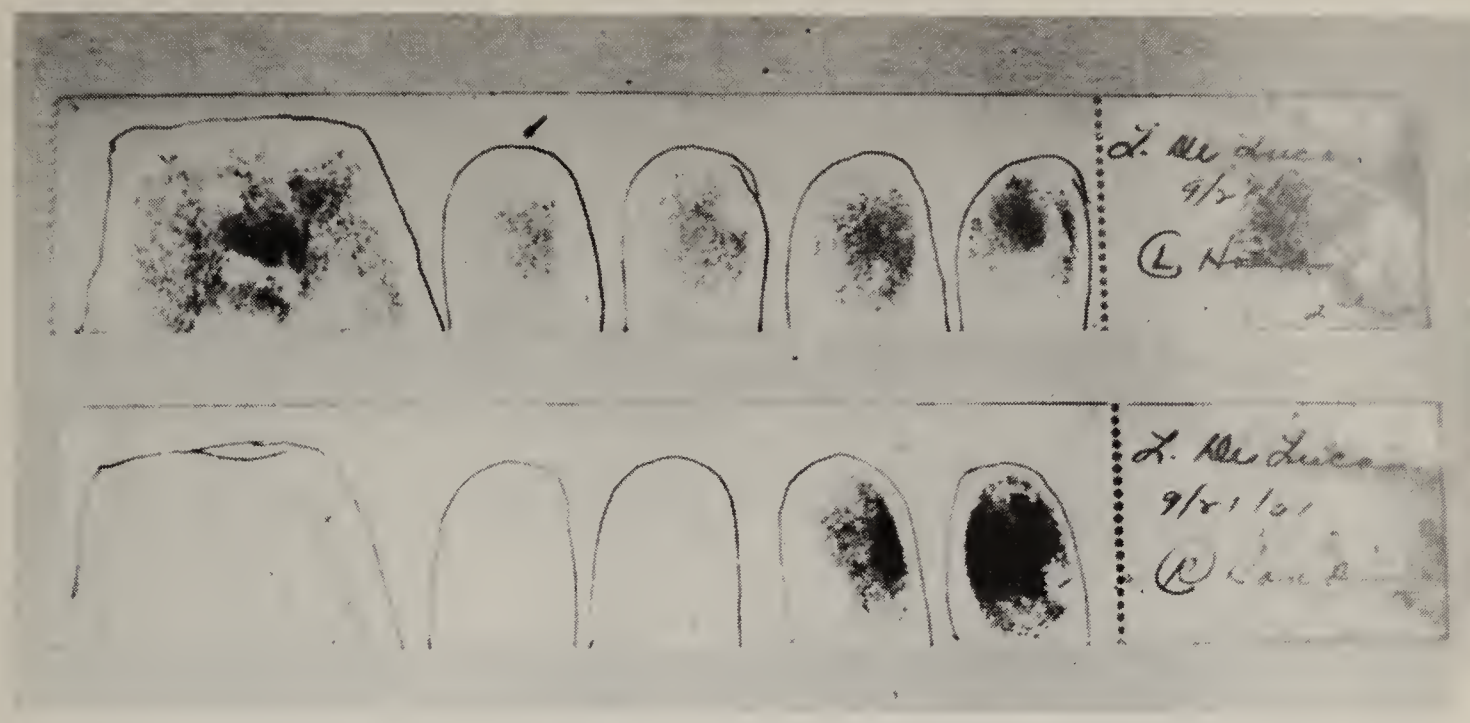

Fig. 5.—Ninhydrin print test of patient in Fig. 4.

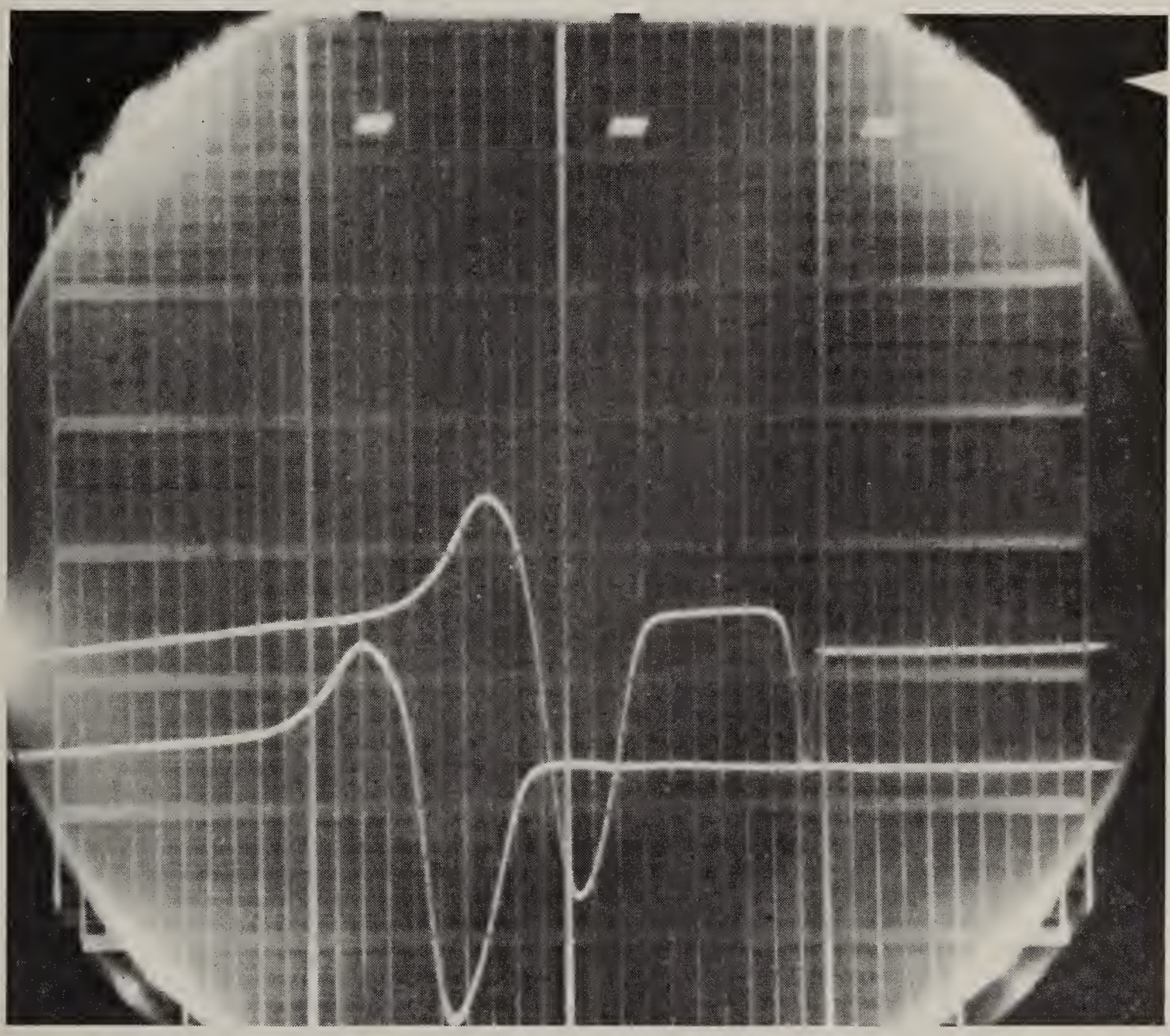

Fig. 6.—Delay in wrist latency time in a patient with a Carpal Tunnel Syndrome (7.5 msec.)

Delayed Repair Versus Immediate Repair

Immediate repair of a lacerated nerve is indicated when the wound is relatively clean, without a crush element, caused by a sharp instrument, and within 6 to 12 hours of the accident. If the injury is seen late, or the nerve repaired inadequately, a neurorrhaphy should be carried out not later than 6 months after the injury. Delay after that time is prejudicial to recovery since the Schwann tubes shrink, the motor end plates atrophy, and fibrosis of muscle occurs. Occasionally, a surgeon may obtain a good recovery with repair after 6 months.

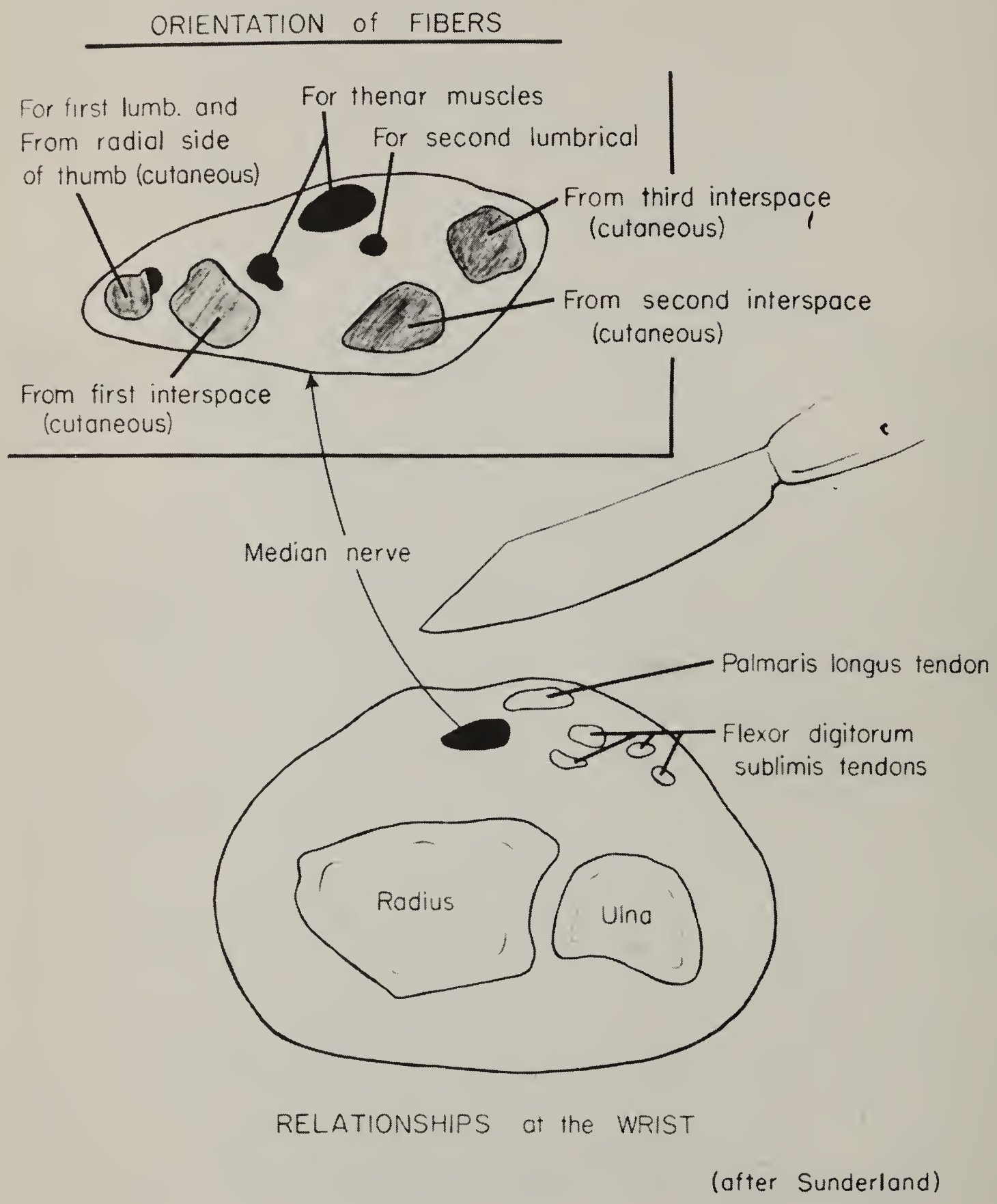

Fig. 7.—Cross section of median nerve fibers at the wrist.

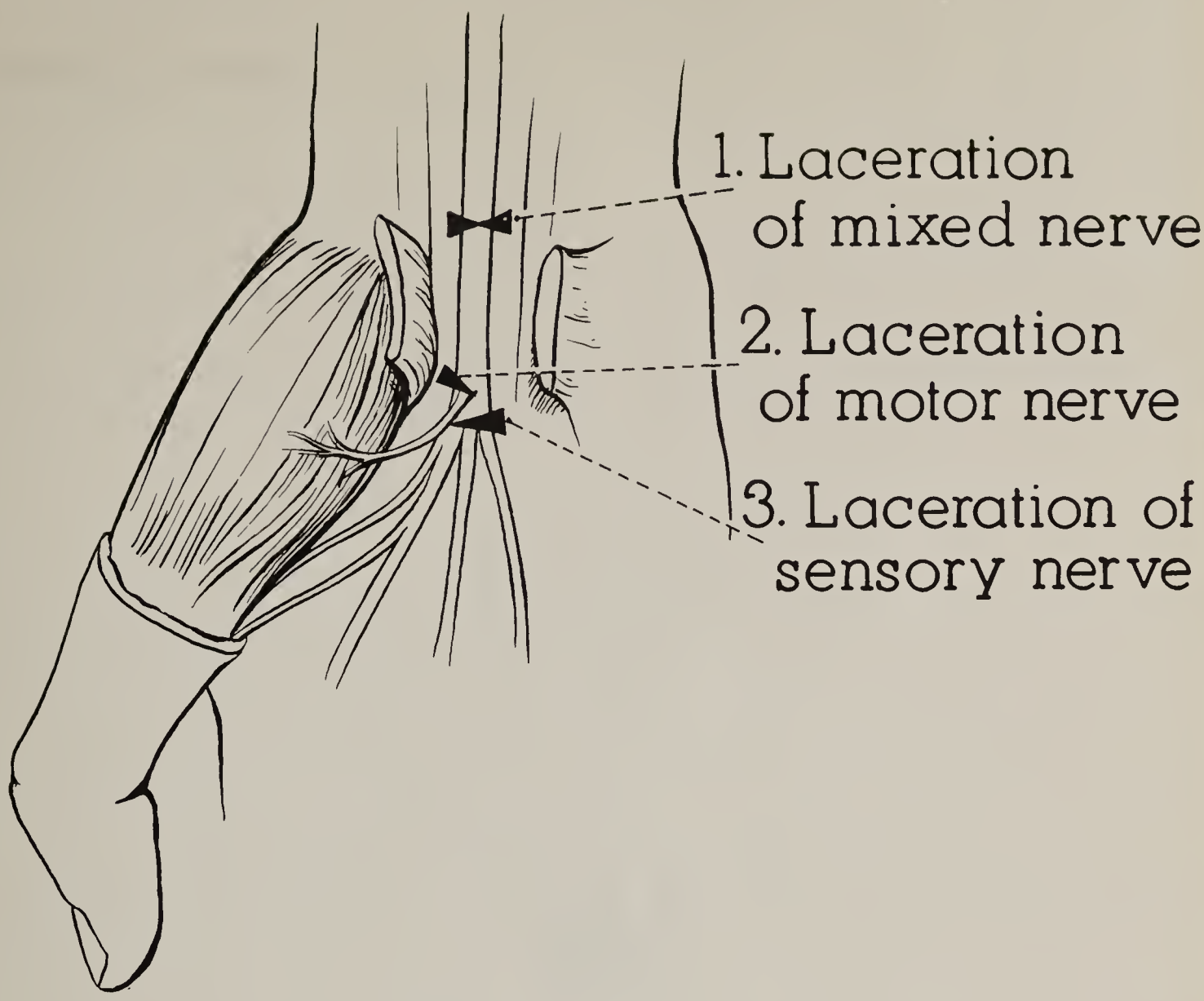

Fig. 8.—Anatomical zones of median nerve lacerations related to technical problems of repair.

Anatomical Problem of Repair

The technical difficulty of repair of the nerve is considerable at times. Repair in Zone 3 is more difficult than in Zone 1 (Fig. 8), because anastomosis of the large proximal nerve stump with the smaller distal stumps disrupts the funicular pattern and results in incongruity. Mobilization of the nerve to bridge a gap may cause devascularization of the nerve resulting in a poor repair.

Combined Tendon and Nerve Injuries

The repair technique should limit the amount of scar about the median nerve. When divided flexor tendons accompany a laceration of the median nerve, it may be necessary to repair only the divided flexor profundus tendons, omitting repair of the flexor sublimis and palmaris longus. Considerable scarring may ensue from reconstitution of these structures if the procedure is unduly complicated or prolonged.

AGE AND PROGNOSIS

Onne has pointed out in his thesis on median nerve injuries in Sweden that complete recovery is rare after repair of a laceration except in children under six years.[1] However, careful evaluation and meticulous surgical technique can improve this prognosis.

CONCLUSIONS

1. Thorough examination is required for all deep lacerations at the wrist. This may require exploration in the operating room.
2. Four tests of sensation are of value in evaluation of the sensation of the hand: ninhydrin, coin, two-point discrimination, and pickup tests.
3. Immediate repair of the lacerated nerve is indicated where possible. When conditions are not optimal, neurorrhaphy can take place in 3 to 6 weeks. A nerve should be repaired before 6 months following injury as irreversible processes jeopardize the result thereafter.
4. The anatomical location of the laceration and the age of the patient, as well as whether the branch of the nerve is pure sensory or mixed motor and sensory, affect the repair and the end result. □

REFERENCES

1. Onne, L.: Recovery of Sensibility and Sudomotor Activity in the Hand after Nerve Suture. *Acta. Chir. Scand.*, Suppl. 300, 1962.
2. Sunderland, S.: The Intraneural Topography of the Radial, Median and Ulnar Nerves. *Brain*, 68:243, 1945.
3. Tanzer, R.: The Carpal Tunnel Syndrome. *J. Bone Joint Surg.*, 41-A:626, 1959.
4. Licht, S., Editor: Electrodiagnosis and Electromyography. 2nd ed., E. Licht, Pub., Baltimore, Md., 1961, p. 392.

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ASYMMETRICAL FUSIONAL VERGENCE: EYE MOVEMENTS RESULTING FROM TARGET MOVEMENT ALONG THE VISUAL AXIS OF ONE EYE

BERT L. ZUBER, PH.D.[1]

INTRODUCTION

Asymmetrical vergence is defined as the pattern of eye movement resulting when the eyes move between any two points in space, provided these points do not lie on the same cyclopian axis and that they are at different distances from the subject. This pattern of eye movements, composed of saccadic and vergence components, has been described in the work of Yarbus.[12] Responses to asymmetrical vergence stimuli may be found in the records of Yarbus,[12] Westheimer and Mitchell,[11] Riggs and Niehl,[8] Alpern,[1] and Alpern and Ellen.[4,5]

One special case of asymmetrical vergence has long been of interest to investigators of oculomotor function, namely, the case where target motion is confined to the visual axis, or line of sight of one eye. Obviously, the eye in whose visual axis the target movement occurs need make no movement whatever in order to maintain perfect fixation of the target. A certain amount of controversy has arisen due to the observation that this eye, under certain conditions, actually moves in a pattern which is correlated with the movement of the fellow eye.[1,4,5] For purposes of the following discussion it will be assumed that target motion occurs along the visual axis of the right eye. Now a very simple condition determines whether the right eye moves. If viewing is binocular, both eyes will move in response to target motion with the following pattern: both eyes will saccade and converge (or diverge as the case may be) concurrently, but the vergence carried out by the right eye will be equal and opposite to the saccade, so that this eye ends up where it started, having made a completely superfluous movement. Such responses are shown in Fig. 1. If viewing is monocular, however, with the left eye occluded, then only the left eye moves to follow the target motion

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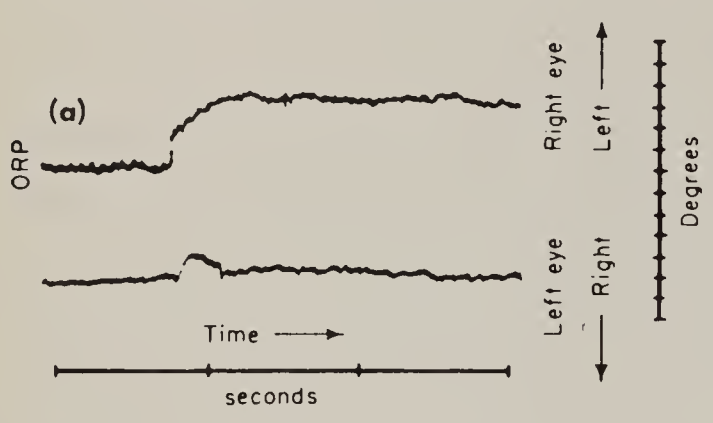
(which it does not see), the right eye stands still. Such a response is shown in Fig. 2. This monocular experiment is called the experiment of Johannes Mueller, after the man who first described it in 1826. Since that time it has been repeated by numerous investigators. The works of Alpern and Ellen[4,5] exemplify such studies.

The controversy has arisen out of the observation that two entirely different patterns of activity of the right eye may be elicited by simply covering the left eye or not. The pattern of movement of the right eye under binocular viewing conditions has been offered as proof that vergence movements, along with versions, obey Hering's Law.[3] In support of this are verifying electromyographic studies.[10]

The puzzlement then is: what happens to Hering's Law when the left eye is covered and the right eye does not move? It is important to note that covering the left eye restricts the subject to the use of accommodative vergence while binocular viewing allows both fusional and accommodative vergence to be used. It may be, then, that accommodative vergence is the only type of eye movement which does not obey Hering's Law. It may be that accommodative vergence is the sole example of "uniocular" eye movement.

It has already been clearly shown that the right eye is immobile when only accommodative vergence is used, and that the right eye moves as predicted by Hering's Law if both fusional and accommodative vergence are used. For a perfect dissection it remains only to show that this same pattern of movement is observed when only fusional vergence is used. Alpern's records[1] show this pattern of movement, but he used prisms placed before the right eye to change the target position for that eye. Under such conditions one cannot be absolutely sure that accommodation is well controlled. In addition, Alpern recorded eye position by the method of electro-oculography, a method allowing rather poor resolution ($\pm 0.5°$) and subject to various artifacts. Alpern has described the limitations of this method.[2] In view of the limits on resolution he had to use relatively large stimuli to fusional vergence in order to obtain a resolvable trace. It has been shown that such large inputs can cause activity in the accommodative system.[6] Alpern's results are shown in Fig. 1 (a). The results of Westheimer and Mitchell[11] using only fusional vergence also show the described pattern, but here again, although a different recording method was used (cor-



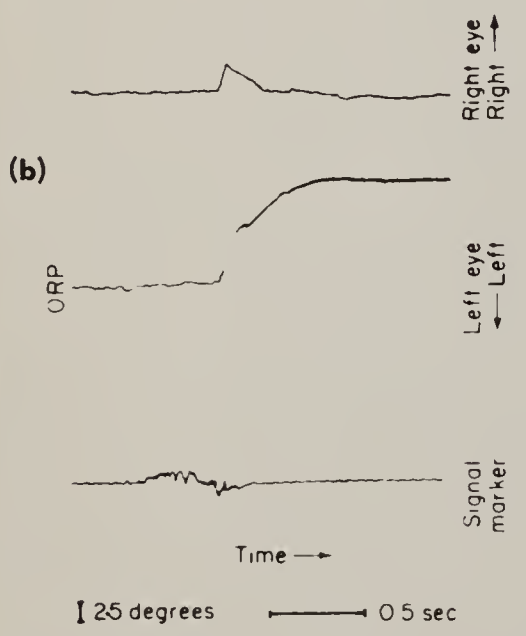


Fig. 1.—(a) Electro-oculographic recording of eye movement when a base-out prism equivalent of 4° of convergence is intruded in front of the right eye with binocular fixation[1]
(b) Record of eye movement when fixation is changed from far to near target along the visual axis of the right eye with binocular fixation[4]

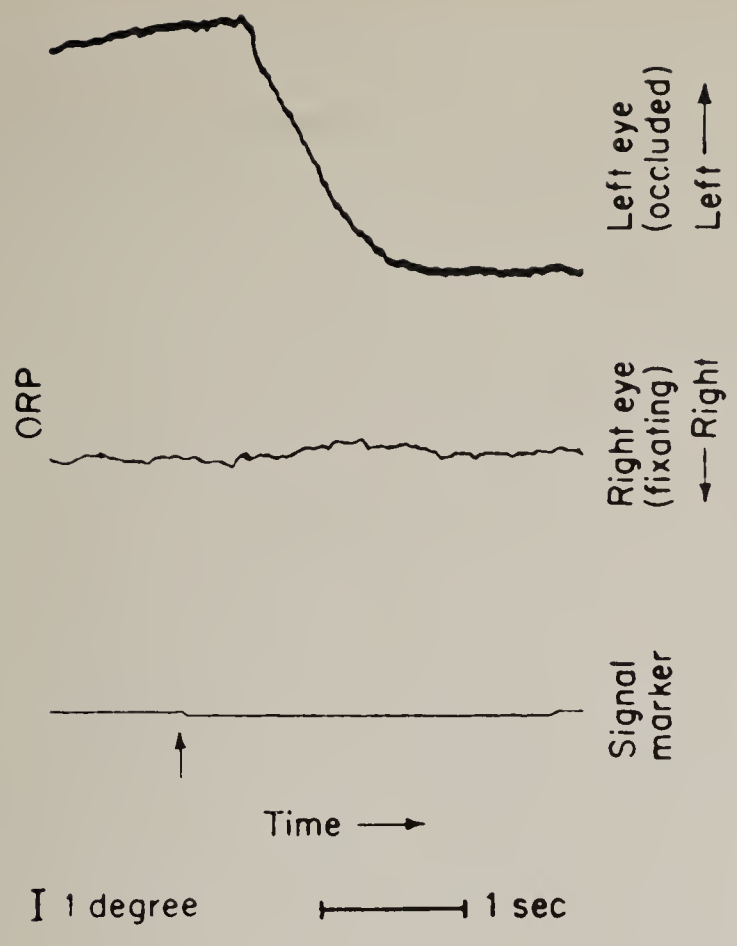


Fig. 2.—Eye movement recorded when fixation is changed from far to near target along the visual axis of the right eye with the left eye occluded. Note that only the occluded eye moves[1]

neal reflection), resolution is relatively poor.

These experiments have, therefore, been repeated using an apparatus similar to that described by Rashbass and Westheimer[7] to stimulate the fusional vergence mechanism. This apparatus is diagrammatically shown in Fig. 3. The subject's head is represented by the circle at the left of the figure; his eyes are the two protrusions from this circle. The subject views the faces of the cathode ray tubes of two oscilloscopes, one directly ahead of him, the other to his right. This latter screen is viewed via a plane mirror which makes an angle of 45° with the subject's median plane. This mirror also serves to prevent the left eye from viewing the right screen and, likewise, to prevent the right eye from viewing the straight-ahead screen. The oscilloscopes are connected in parallel, and small identical spots (0.2° in diameter) are projected on their cathode ray tubes. The spots are positioned on corresponding loci of the two screens with the result that the subject turns each eye so that the images of the spots fall on the foveas. The images are fused and the subject sees one spot at the apparent distance corresponding to the intersection of his two lines of sight. Since the subject's lines of sight pass through the spots (in the case of the right eye, the image of the spot on the mirror) the amount of convergence required for fusion is a function of the horizontal position of the spots on the screens. As Fig. 3 indicates, the range of apparent distances available with this apparatus is from 150 cm (1.2° of convergence, spots at extreme left of screens) to 10 cm (16.6° of convergence, spots at extreme right of screens). Within this

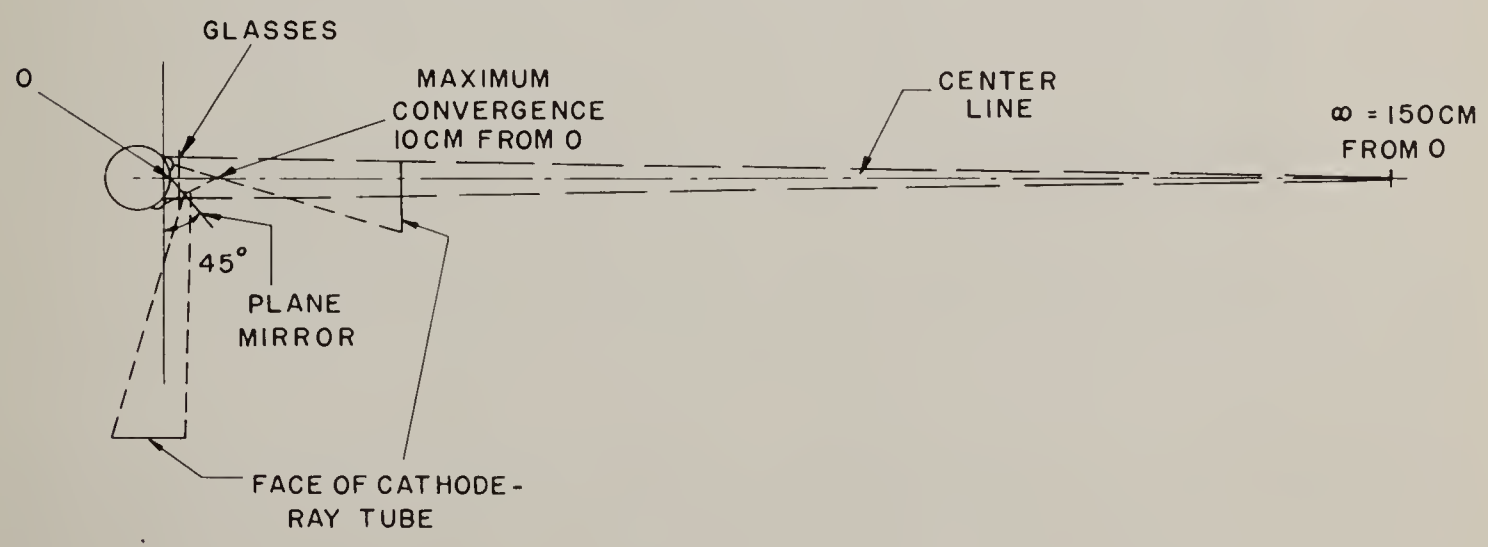


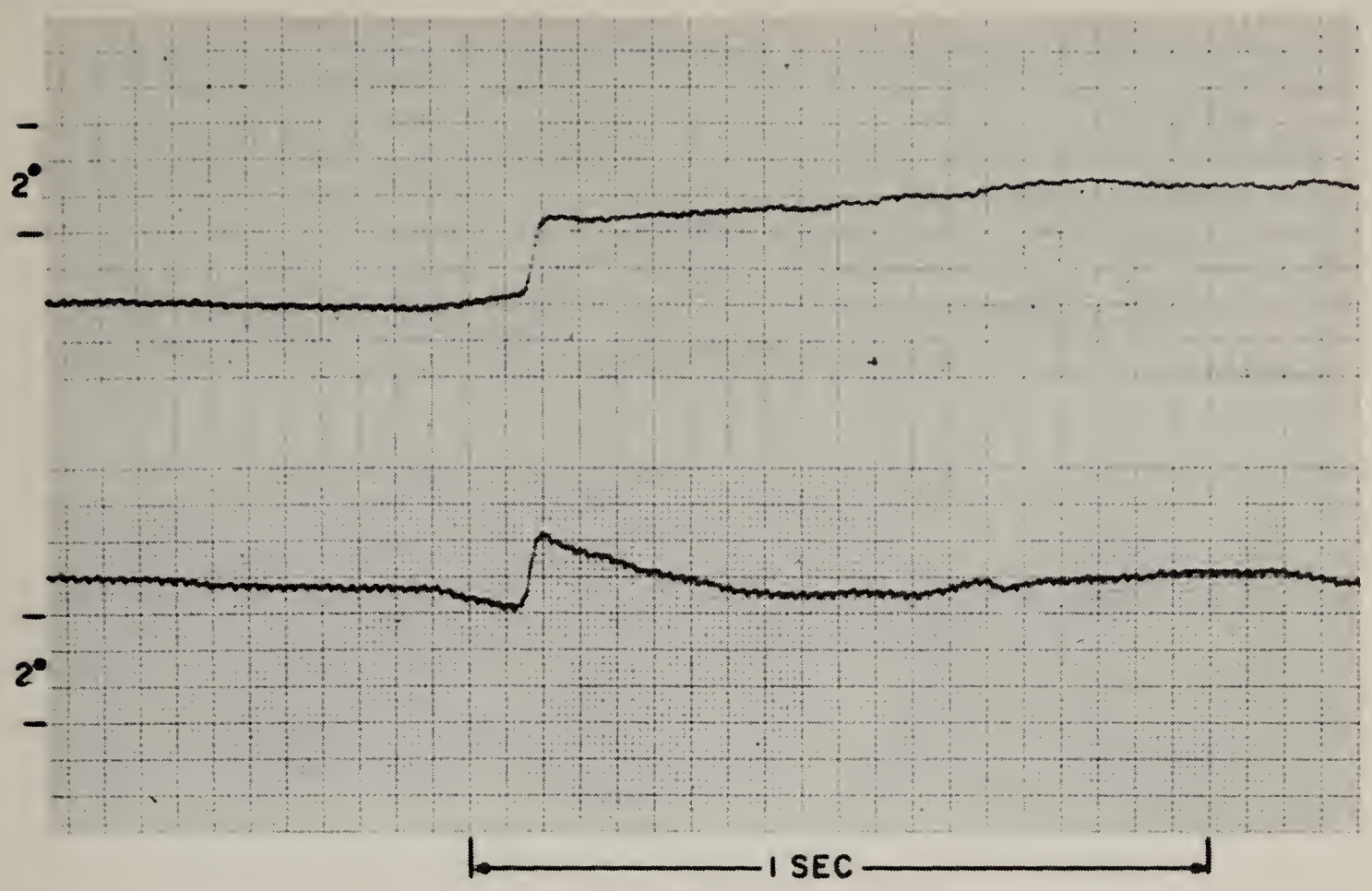
Fig. 3.—Diagram of the apparatus used for stimulating the fusional vergence system

range 1 cm of spot movement corresponds to 1.7° of vergence. The spots may be driven with any waveform selected by the experimenter, and the subject is asked to keep the spots fused. In the process of maintaining fusion the subject's eyes follow the movement of the target. This is such a natural process that only the experienced subject can voluntarily break fusion once it has been achieved. Of course, during target movement both spots will be seen separately if the movement of the eyes happens to lag behind the movement of the spots. Whether the subject in fact experiences diplopia depends on the extent of the lag.

In this case the experiment is simple. The spot on the cathode ray tube viewed by the right eye is held stationary by disconnecting the input to that scope. The other spot (viewed by the left eye) is moved in stepwise fashion. The movements of both eyes are recorded with high resolution by a technique involving differential reflection of infrared light from the sclera and iris[9,13] and 2° stimuli are used to avoid accommodative interactions. A typical response is shown in Fig. 4. The lower record shows control responses to a .25 cps square wave stimulus to midline vergence. Notice that both eyes converge (traces converging) and diverge (traces diverging) by the same amount and that there are no saccadic components. For reference a series of saccades occurring between vergence responses appears on this control record. Left eye position is shown on the upper trace, right eye position on the lower trace. The upper record shows the responses of both eyes to a step stimulus to asymmetrical fusional divergence occurring some 200 msec before the response and along the visual axis of the right eye. Notice that the vergence begins before the saccadic component. During and after the saccade vergence continues. The net result of the response is that the left eye (upper trace) has assumed its new position, while the right eye (lower trace) has moved with equal and opposite saccadic and vergence components to assume the same position that it had before the response occurred. The results of this experiment, then, clearly confirm those of Westheimer and Mitchell[11] and Alpern.[1] They furthermore show that the responses to fusional vergence stimuli along the visual axis of one eye occur with the same pattern of movements described by Yarbus[12] for other types of asymmetrical vergence.

It seems clear that the complex saccadic-vergence response is associated with the fusional mechanism, for it does not occur when only accommodative vergence is used. This raises some questions as to the nature and purpose of accommodative vergence. In order to determine if accommodative vergence is truly monocular in nature it would be interesting to see if the two eyes could be disassociated and separately driven by different accommodative inputs to each eye. In some normal situations the accommodative inputs to each eye are considerably different. Consider the case where a person fixates a close object off to one side. In such a case the distance of the target from each eye, which is presumably related to the accommodative input, may be quite different. In such a situation, which ocular input controls the vergence level? Or is it possible that the level for each eye is separately controlled by the accommodative vergence input for that eye?

It is always stated that saccadic movements are exactly the same angular magnitude for each eye. The work of Yarbus[12] shows that vergence movements also tend to be equal (but opposite) for each eye. When the targets are reasonably distant from the subject ($>$ 1 m.) the geometry of the object space is such that any object may be fixated with sufficient accuracy by a series of equal eye movements. When target distances are short, however, significantly different movements may be required by each eye to fixate a new target. For example, if a target moves from a distance of 25 cm to 15 cm along a cyclopian axis which makes an angle of 45° with the median plane, then, in order to maintain fixation, the left eye must converge by



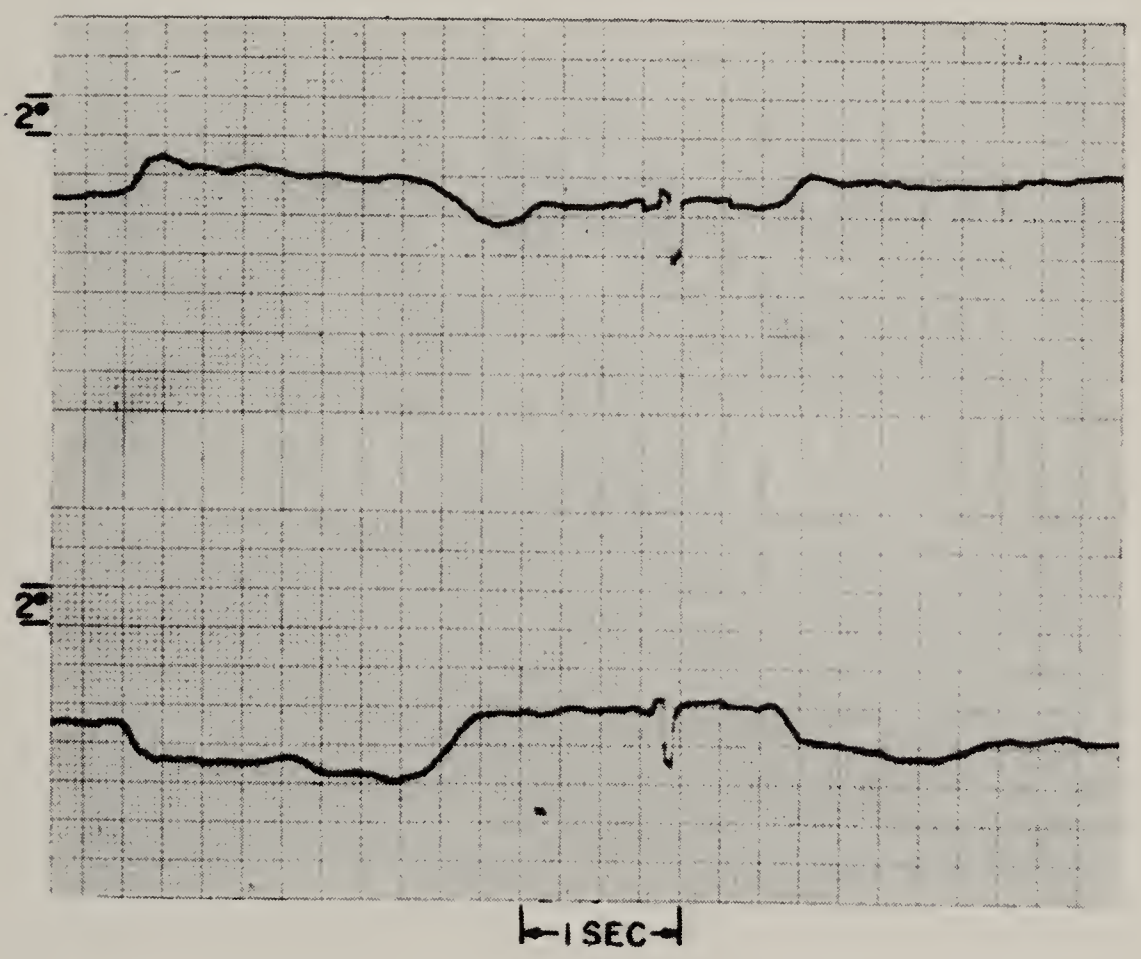


Fig. 4.—An asymmetrical fusional divergence response to stepwise target movement along the visual axis of the right eye (upper record). Lower record shows midline vergence controls

6.2° while only 5.2° of convergence is required by the right eye. These differences arise simply because the eyes are not located at the same point in space. It would be of interest to know what sort of strategy is employed by the oculomotor system under such conditions. It may be that one eye (dominant eye?) is used as a reference, maintaining perfect fixation, while the proper position of the other eye is determined by accommodative vergence. Such questions cannot be answered at present, but they do suggest a number of interesting and illustrative experiments.

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SUMMARY

Using a small yet unequivocal stimulus to fusional vergence and a sensitive method of recording eye position it has been shown that the response to stepwise target motion along the visual axis of one eye consists of compound saccadic-vergence movements of both eyes. This type of response is seen under a variety of viewing conditions, but only when the fusional mechanism is utilized. It is suggested that such a response may represent a functional and perhaps mechanistic division of the fusional and accommodative vergence eye movement systems. Some questions regarding the function of accommodative vergence eye movements are raised.

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REFERENCES

1. Alpern, M.: The Position of the Eyes During Prism Vergence. AMA Arch. Ophthal., 57:345, 1957.
2. Alpern, M.: Types of Movement in the Eye. Vol. 3, Muscular Mechanisms, H. Davson, Ed. Academic Press, N.Y., 1962, p. 67 et seq.
3. Ibid., p. 93.
4. Alpern, M. and Ellen P.: A Quantitative Analysis of the Horizontal Movements of the Eyes in the Experiment of Johannes Mueller I. Method and Results. Amer. J. Ophthal., 42:289, 1956.
5. Alpern, M. and Ellen, P.: A Quantitative Analysis of the Horizontal Movements of the Eyes in the Experiment of Johannes Mueller II. Effect of Variation in Target Separation. Amer. J. Ophthal., 42:296, 1956.
6. Fry, G. A.: Further Experiments on the Accommodation-Convergence Relationships. Amer. J. Optom., 16:325, 1939.
7. Rashbass, C. and Westheimer G.: Disjunctive Eye Movements. J. Physiol., 159:339, 1961.
8. Riggs, L. A. and Niehl, E. W.: Eye Movements Recorded During Convergence and Divergence. J. Opt. Soc. Amer., 50:913, 1960.
9. Stark, L. and Sandberg, A.: A Simple Instrument for Measuring Eye Movements. QPR 62, Research Laboratory of Electronics, M.I.T., p. 268, 1961.
10. Tamler, E., Jampolsky, A. and Marg, E.: An Electromyographic Study of Asymmetric Convergence. Amer. J. Ophthal., 46:174, 1958.
11. Westheimer, G. and Mitchell, A. M.: Eye Movement Responses to Convergence Stimuli. AMA Arch Ophthal., 55:848, 1956.
12. Yarbus, A. L.: Motion of the Eye on Interchanging Fixation Points. Biofizika, 2:698, 1957.
13. Zuber, B. L., Michael, J. A. and Stark, L.: Visual Suppression During Voluntary Saccadic Eye Movements. QPR 73, Research Laboratory of Electronics, M.I.T., p. 217, 1964.

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BOOK REVIEW

ANTICANCER AGENTS by Frances E. Knock, Ph.D., M.D. (*Am. Lecture Series, Ed. 1*) *Charles C. Thomas, Pub.: Springfield, Ill., 292 pg., 140 illus., $15.50.*

F. E. Knock attacks cancer from a broad basis of natural philosophy, with a good knowledge of chemistry. She touches on most problems connected with cancer research and therapy, like prevention, early diagnosis, localized and generalized treatment, surgery, radiation, chemotherapy, with all the various sidelines. She does this with extensive theoretical and practical knowledge and experience.

The book contains many ideas, two of which stand in the foreground. The one is based on the fact that cancer varies in its sensitivity towards various drugs a great deal. One case may respond well to a certain drug while another may be refractory, and be sensitive to a different therapy. So it seems logical to collect information about the sensitivity of a cancer before a therapy is applied. This can be done by treating a sample of the cancer, obtained through biopsy, with various drugs, in order to get information about its reaction. A simple method is given, based on the reduction of dyes. This procedure may spare the patient much suffering but its results are less accessible to a simple statistical evaluation. Such a statistical approach is rendered even more difficult by the adjuvants advocated. While statistics may suffer, the patient may gain, and it is a matter of philosophy which side one takes.

The other basic idea is that sulfhydryl groups of various cell constituents may offer a very hopeful target for chemotherapeutic agents. Reviewer fully shares this idea, having obtained indication that nature herself regulates cell division by means of acting on the SH groups.

The book recommends itself also by its freshness of approach, the great number of ideas, as well as by its beautiful typography.

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Institute for Muscle Research at the
Marine Biological Laboratory,
Woods Hole, Massachusetts

ABSTRACTS AND REVIEWS

OF PUBLICATIONS BY THE STAFF

Deinhardt, F. and Deinhardt, J.: The Use of Platyrrhine Monkeys in Medical Research. Some Recent Developments in Comparative Medicine. *Symposia of The Zoological Society of London, 17:127-159, 1966.*

The phylogeny, availability, laboratory maintenance, disease hazards and use of platyrrhine monkeys in medical research, with special reference to the use of the Callithricidae.

Holmes, A. W.; Devine, J. A.; Nowakowski, E.; and Deinhardt, F.: The Epidemiology of a Herpes Virus Infection of New World Monkeys. *J. Immun., 90:4, 668-671, 1966.*

Data are presented which indicate that the virus previously reported as marmoset herpes virus (Herpesvirus tamarinus) is an agent which produces nonfatal infection in nature in other New World Monkeys. It is suggested that the course of infection in these or other monkeys may mimic herpes simplex infection in the human.

Hass, G. M.; Landerholdm, W.; and Hemmens, A.: Production of Calcific Atheroarteriosclerosis and Thromboarteritis with Nicotine, Vitamin D and Dietary Cholesterol. *Amer. J. Path., 49:739-771, 1966.*

Rabbits fed sufficient cholesterol to maintain average serum cholesterol levels at near 350 milligrams percent for about 4-8 months developed no arterial disease other than innocuous aortic intimal atheromata. When this regimen was supplemented either with 50,000 I.U. of vitamin D_2 intramuscularly twice every fourth week or with intramuscular doses of nicotine in oil (increasing from about 5 to 20 milligrams) twice each week, the arterial disease was unchanged. If, however, these three regimens were concomitant, a severe generalized calcific fibroatheromatous arterial disease developed. This disease was often complicated by thromboarteritis, restricted principally to small arteries supplying smooth and skeletal muscle. Occlusive fibrinous thrombi in arteries with luminal diameters of about 250 to 500 microns became organized and canalized. Fibrinous thrombi in smaller arteries were resolved by lysis. These observations direct attention to mechanisms by which neuro-humoral factors may participate in the pathogenesis of arteriosclerosis and its thrombotic complications.

Clasen, R. A.; Pandolfi, S.; Laing, I.; Oelke, D.; and Hass, G. M.: Reserpine in Experimental Cerebral Edema. *Neurology, 16:1194-1204, 1966.*

Focal areas of hemorrhagic necrosis were produced in the brain of anesthetized monkeys. The animals were observed for a period of twenty-four hours, after which they were sacrificed and the cerebral hemispheres analyzed chemically for their electrolyte and water content. The uptake of RISA and Evan's blue was also determined. A second group of animals was treated with reserpine beginning one hour after injury. No unequivocal evidence that this form of therapy reduced the edema associated with these lesions was obtained, although a difference in the relationships of the variables was observed.

Dolowy, W. C.; Henson, D.; Cornet, J.; and Sellin, H.: Toxic and Antineoplastic Effects of L-Asparaginase: Study of Mice with Lymphoma and Normal Monkeys and Report on a Child with Leukemia. *Cancer, 19:1813-1819, December, 1966.*

L-Asparaginase has been shown to exert an antitumor effect against certain animal tumors by depriving the tumor cell of an adequate supply of L-asparagine by converting L-asparagine to aspartic acid and ammonia in vivo.

Partially purified guinea pig serum L-asparaginase was active against subcutaneous lymphomas in mice, but whole guinea pig serum was not effective against intracerebral tumors. No toxic effects occurred after administration of partially purified L-asparaginase in mice with small tumors or in monkeys. Profuse diarrhea occurred in mice with massive tumors after treatment, during tumor regression.

L-Asparaginase was administered intravenously to one 8-year-old boy with a 3-year history of acute lymphoblastic leukemia.

During infusion, the temperature rose from 99 to 104°F, the pulse from 150 to 190/min., the respiratory rate from 36 to 60 at 2 hours. Blood pressure fell from 120/80 to 90/50 at 5 hours, hematocrit fell from 21 to 15 in 4 hours.

Subsequently, the total WBC decreased from 18,000 to 4,700/mm^3, the lymphoblasts decreased from 67% to 14%, the liver decreased from 8 to 3 cm beneath the costal margin and a tumorous testicle decreased from 7.5 x 9 cm to 4 x 5 cm.

Ten days after treatment, the patient died with pulmonary hemorrhage and focal leukemic infiltrates in the meninges, brain, liver, spleen, marrow and testis.

Long, D. M.; Hartmann, J. F.; and French, L. A.: The Ultrastructure of Human Cerebral Edema. *J. Neuropath. Exp. Neurol., 25:373-395, 1966.*

The literature dealing with the morphology of cerebral edema has been reviewed. Cerebral edema has been studied electron microscopically in 18 patients in an attempt to define exactly the characteristics of human cerebral edema and to correlate the ultramicroscopic findings with the accepted light microscopic abnormalities. These characteristics have been described. The light and electron microscopic descriptions of cerebral edema have been compared and have been found to be quite compatible. The theories concerning the functional abnormality in cerebral edema have been briefly reviewed. On the basis of the morphologic characteristics it is postulated that the abnormality lies at the capillary-glial interface. The analogies supporting this hypothesis are reviewed.

Long, D. M.; Hartmann, J. F.; and French, L. A.: The Response of Human Cerebral Edema to Glucosteroid Administration. An Electron Microscopic Study. *Neurology, 16:521-528, 1966.*

A morphological description of the effect of dexamethasone, a potent glucosteroid, upon cerebral edema occurring in fifteen patients has been presented. The ultrastructural characteristics of edema have been reviewed and changes in this edema after dexamethasone administration described. Dexamethasone definitely reduces the amount of brain swelling, particularly in terms of astrocyte cytoplasm and the extracellular accumulation of fluid in the white matter. The edematous brains are returned toward a normal configuration by the administration of the drug. A hypothesis for a mechanism of action of the steroid is presented.

Long, D. M.; Hartmann, J. F.; and French, L. A.: The Response of Experimental Cerebral Edema to Glucosteroid Administration. *J. Neurosurg., 24:843-854, 1966.*

Dexamethasone and other glucosteroids are known to be of value in the treatment of patients suffering from cerebral edema. The histological changes which accompany the resolution of the signs and symptoms of cerebral edema following therapy have not been previously studied. We have shown that dexamethasone will prevent the ultrastructural characteristics of experimental cerebral edema from developing. The administration of the drug after the appearance of the signs and symptoms of brain swelling is effective in reducing the amount of structural abnormality present. We have reviewed the ultrastructural characteristics of cerebral edema and have given a possible explanation for the action of dexamethasone.

Hartmann, J. F.: High Sodium Content of Cortical Astrocytes. Electron Microscopic Evidence. *Arch. Neurol., 15:633-642, 1966.*

The cerebral cortex from normal rats and from those treated with diphenylhydantoin and desoxycorticosterone acetate has been studied in the electron microscope after fixation by a method designed to precipitate sodium in cells and tissues. In all animals, the astrocytes have been found to have a high concentration of precipitate, with much smaller amounts being present within cisterns of endoplasmic reticulum and in other restricted sites in neurons and oligodendroglial cells. Treatment of animals with the combination of drugs mentioned results in a detectable depletion of precipitate in neurons and in those astrocytic processes that adjoin synaptic terminals. The chemical identity of the precipitate as sodium antimonate is shown by this experiment and by electron diffraction studies. The results of the present study strongly suggest that astrocytes collectively constitute an intracellular fluid compartment for distribution of ions within the cerebral cortex. They also help to explain the discrepancy currently existing between the size of the extracellular space as measured by ultrastructural studies and as determined by such indirect methods as impedance techniques, because in the latter case most or all of the cortical sodium has been assumed to be extracellular.

Hartmann, J. F.: Ultrastructural Relationships of Neuronal Cytoplasmic Membranes. *Med. Biol. Illus., 16:109-113, 1966.*

The endoplasmic reticulum has been observed by numerous investigators to be structurally continuous with the outer layer of the nuclear envelope in various cell types. Continuity between reticulum and plasma membrane has also been reported, suggesting an uninterrupted, albeit tortuous, channel connecting extracellular space with the nuclear perimeter. Morphological evidence for such continuity is, however, scarce and has dealt with either tumor cells or absorptive epithelium. The present report presents evidence suggesting extreme rarity or total absence of such a continuous channel in cortical neurons. Confluence of the space between layers of the nuclear envelope with that between membranes of endoplasmic reticulum is observed with great regularity, but diligent search for a comparable confluence at the cell surface has been unrewarding. Instead, the pouches of endoplasmic reticulum appear to end blindly as attenuated sacs or tubules parallel and immediately subjacent to the plasmalemma (subsurface cisterns of Rosenbluth). The finding of such cisterns in cortical neurons situated most often in relation to abutting protoplasmic astrocyte processes invites speculation regarding their possible role in transport mechanisms of central nerve tissue.

Clawson, C. C.; Hartmann, J. F.; and Vernier, R. L.: Electron Microscopy of the Effect of Gram-negative Endotoxin on the Blood-brain Barrier. *J. Comp. Neurol., 127:183-198, 1966.*

Studies with the light microscope indicated that an injection of endotoxin into the carotid artery of a rabbit alters the blood-brain barrier allowing the distribution of subsequently injected colloidal iron throughout the cerebral cortex. The present investigation by electron microscopy determined the distribution of the colloidal iron oxide in the normal and endotoxin altered cerebral capillaries of rabbits. Four hours prior to the intracarotid injection of saccharated iron oxide the animal received an injection via the same artery of either 50ug gram-negative endotoxin or a control dose of normal saline. The animals were sacrificed at times from 15 minutes to two hours after the injection of iron oxide and samples of the cerebral cortex were processed for electron microscopy by routine methods. In those animals that did not receive endotoxin, the colloidal iron was limited to the lumen of the cerebral capillaries and occasional large endothelial vacuoles. None of the iron was found in the endothelial pinocytotic vesicles. In the endotoxin animals the iron oxide particles were found

in quantity in the capillary endothelium phagosomes, the basement membrane, and in astrocytes and their processes. The fine structure of the cerebral capillary is reviewed and evidence is presented in support of the hypothesis that the barrier mechanism for colloidal tracers lies in a unique property of the brain's endothelial pinocytotic vesicles.

Apter, J. T. and Skaggs, L. S.: The Effects of Hypertension on Pressure. *Proceedings of the Symposium on Biomedical Engineering, Rochester Minn., 1:369-372, July 22-27, 1966.*

A mathematical model consistent with the visco-elastic behavior of the aorta and arterioles was developed to include 3 non-linear parameters. The model was amenable to analytic solution for only a portion of the cardiac cycle and only if gross approximations were made for the ventricular inflow curve. In contrast, the analogue computer permitted solution of the equations to generate aortic pressure curves closely resembling real ones and also called attention to the significance of some details of the diastolic portion of the curve which had previously been attributed to artefacts or overlooked altogether.

Curtin, J. W.; Holinger, P. H.; and Greeley, P. W.: Blunt Trauma to the Larynx and Upper Trachea: Immediate Treatment, Complications and Late Reconstructive Procedures. *J. Trauma, 6:4, 493-501, June 1966.*

Automobile accidents are responsible for the increased frequency of laryngeal injury and in particular fractures of the larynx and trachea. In a previous summary of our experiences 43 of 82 laryngeal fractures were reported as having occurred in transportation vehicles.

Since 1959, 34 additional patients with severe laryngeal and tracheal trauma have been seen. Over half of these patients treated required extensive external and internal laryngeal or cervical tracheal reconstruction or both because of stenosis or atresia.

This presentation details: 1) the management of the acute injury to avoid serious complications; and 2) late reconstructive procedures, using skin graft, pedicle flap and cartilage graft support, which follow the removal of deforming scar tissue contractures.

Curtin, J. W. and Ellenby, J. D.: Guidelines in Medical and Forensic Management. *J. Plast Reconstr. Surg., 38:4, 8-15, October 1966.*

Occasional untoward events occur during hospitalization, which pose medicolegal problems. Generally, these incidents result in frequent private discussions but infrequent public presentation for professional review. Such occurrences may involve physicians, nurses or auxiliary hospital employees, and eventually encompass the duties of various administrative personnel. Because these incidents usually produce visible cutaneous lesions, they may fall into the realm of the plastic surgeon for consultation, therapy, or both. Although many adverse situations arise from common, longstanding hospital procedures, others have arisen which are attributable to the increasing complexity of modern medicine and its more sophisticated instrumentation. Illustrated cases occurring during the past few years have been collected and reviewed, and are presented in an attempt both to alert hospital personnel to possible dangers to patients, and to formulate guidelines in their medical and forensic management.

Middleton, A. G. and Curtin, J. W.: Keratoacanthoma or Squamous Cell Carcinoma? A Surgeon's Dilemma. *J. Plast. Reconstr. Surg., 38:1, 56-53, September 1966.*

The problem in establishing an accurate clinical and pathological diagnosis of keratoacanthoma has been difficult. The differential diagnosis between this condition and squamous cell carcinoma depends on clinical as well as microscopic criteria. The surgeon's dilemma becomes more acute when one considers the wide spectrum of opinion among competent pathologists.

The characteristics of keratoacanthoma and its variants are described and compared against squamous cell carcinoma. One of the representative cases is an enormous extensive and invasive lesion of the entire left half of the face. It illustrates the difficulty but therapeutic importance of distinguishing between these lesions.

Curtin, J. W.: Basic Plastic Surgical Principles in Repair of Facial Lacerations. *Illinois Med. J., 33:10, 1625-32, October 1966.*

In the treatment of facial trauma an evaluation of the entire patient must be made in order to establish proper priority of management. An adequate airway must be established and shock corrected before repair of the facial lacerations. Adequate anesthesia (local or general) is mandatory for cleansing of and proper inspection of the wound and reapproximation of the wound in layers. The use of fine instruments and atraumatic technique will assure a good final result in an anatomical area where a rich blood supply is our greatest ally.

Included in the article are numerous illustrations depicting the incorrect and correct methods of approaching major and minor facial lacerations.

Cole, E. R.; Koppel, J. L.; and Olwin, J. H.: The Hydrolysis of Phenylalanine Methyl Ester by Bovine Thrombin. *Canad. J. Biochem., 44:1051, July, 1966.*

Thrombin, usually regarded as a trypsin-like enzyme capable of hydrolyzing only esters of the amino acids arginine and lysine, was found to hydrolyze certain other amino acid esters which are considered specific chymotrypsin substrates. L-Phenylalanine methyl ester inhibited the activation of purified bovine prothrombin by autoprothrombin C, Ac-globulin, phospholipid, and calcium. It was subsequently shown that thrombin is capable of hydrolyzing L-phenylalanine methyl ester or L-tyrosine ethyl ester. This activity developed simultaneously with fibrinogen clotting activity during activation of purified bovine prothrombin in 25% sodium citrate solutions. Moreover, the activity was closely associated with clotting activity on subsequent chromatography on DEAE-cellulose and Amberlite IRC-50 resin columns. All preparations of bovine thrombin, representing a wide range of purity, which have been examined, exhibited this hydrolyzing activity toward L-phenylalanine methyl ester. Further evidence linking this esterase activity with fibrinogen clotting activity was obtained when both activities were inhibited by 2-nitro-4-carboxyphenyl-*N*, *N*-diphenylcarbamate, an inhibitor of chymotrypsin.

Knock, F. E.: Pyruvaldehyde in Cancer Chemotherapy. *Lancet, 1:824, 1966.*

Clinical use of selected SH inhibitors, in accord with results of sensitivity tests on each patient's own cancer, has resulted in objective regression of a variety of human cancers, without deleterious effects on wound healing or hematologic status.

Reaction of SH inhibitors with hindered or inaccessible protein-SH groups may cause more significant structural change in protein than does reaction with accessible protein-SH groups. To titrate hindered protein-SH groups, a detergent like sodium lauryl salfate is often useful. Similarly, in sensitivity tests against a variety of human cancer cells over the past three years, activity of selected SH inhibitors has often been potentiated significantly by adjuncts, especially unstable complexes of pyruvaldehyde. Pyruvaldehyde and other selected SH inhibitors attack human cancers preferentially relative to normal cells of origin, in sensitivity tests against a variety of carcinomas (epidermoid and adenocarcinomas), sarcomas and lymphomas. The promise of the SH inhibitor pyruvaldehyde has now been confirmed by work of Szent-Gyorgyi and associates on isolation and analysis of Retine, apparently a somewhat universal growth regulator deficient in cancer cells, which is believed to contain pyruvaldehyde as active component, or a related ketoaldehyde.

Histochemical studies have shown that pyruvaldehyde and related compounds can act as effective sulfhydryl inhibitors for protein-SH groups of human cancers that have been found clinically to be sensitive to SH inhibitors plus adjuncts.

Knock, F. E.: Protein-Sulfhydryl Groups in Cancer and Gene Control. *J.A.M.A., 197:151, 1966.*

Almost an order of magnitude appears to separate clinical effects of selected SH inhibitors from those of other common anticancer drugs. Whereas the margin is narrow between effective anticancer dose and mortality for drugs like 5-FU, selected SH inhibitors are used immediately after major cancer surgery and have produced regression of a variety of human cancers without injury to wound healing or hematologic status. Patients with leukocyte counts as low as 1,200/ cu mm, platelet counts as low as 11,000/ cu mm, have been treated with the SH inhibitors with improvement in their hematologic status.

Cancer probably involves deranged regulation and regulators of DNA synthesis. Most known carcinogens and anticancer agents react avidly with SH and more avidly with SH than with nucleic acids or their regulators heretofore suggested like histones. In protein-SH groups and their anions, extreme reactivity as nucleophile, in free radical reactions and in forming intermolecular and intramolecular complexes is combined with exquisite sensitivity of reaction to modulations of intimate, submicroscopic chemical milieu. Thereby, the requisite chemical sensitivity for potential fine control of genes by residual protein-SH is introduced, as well as points of attack for an almost endless array of adventitious carcinogens. Either DNA mutations or carcinogens may derange such SH-bearing regulators to increase availability or concentration of appropriately reactive SH groups and thereby enhance sensitivity of human cancers to attack by selected SH inhibitors.

Cherniack, N. S. and Carton, R. W.: Factors Associates with Respiratory Insufficiency in Bronchiectasis. *Amer. J. Med., 41:562, October, 1966.*

Lung volumes, ventilation characteristics, diffusing capacity, mechanics and blood gases were studied in forty-two patients with cylindrical and saccular bronchiectasis proved by bronchography. Thirty-two of these patients had been followed closely for three or more years with repeated tests of pulmonary function, clinical examinations and sputum cultures. Eighteen of these had been observed for as long as seven years. The results show that even patients with localized disease may have significant abnormalities in lung function. Lung function deteriorates as the disease becomes more extensive. The persistent presence of Hemophilus *influenzae* in the sputum is associated with a further reduction in the maximum breathing capacity, but not in the other tests of long function. The degree of measured functional impairment is unaffected by the type of bronchiectasis. In all patients followed carefully the rate of deterioration of pulmonary function with time is slight whether or not antibiotics are taken daily.

Dickson, J. F. III, and Stark, L.: Remote Real-Time Computer System for Medical Research and Diagnosis. *JAMA, 196:11, 149-154, June 1966.*

A real-time digital computer system at Massachusetts Institute of Technology that is useful in medical research and diagnostic studies recently has been placed under the remote teletypewriter control of investigators in hospital laboratories. While the studies to date have been largely concerned with the analysis of neurological control systems, the technique is suitable for the investigation of a wide variety of biomedical problems.

Stark, L; Dickson, J.F. III; Whipple, G.H.; and Horibe, H.: *Ann. NY Acad. Sci., 126:851-72, 1965.*

The hardware and software aspects of a system for the remote, on-line, real-time computer diagnosis of electrocardiograms have been presented. Particularly accented are the use of a multiple adaptive matched filter technique for morphological pattern recognition and an executive monitoring routine that provides the hospital technician with remote teletype control of the system.

In discussion, note is made of some of the areas that have been investigated in the course of the development of this system and of those which are now going on or are being planned in the interest of improving specific aspects of the system. Particularly, current efforts are being made to extend the diagnostic capabilities of the system by increasing the fidelity of the adaptive matched filter, by the development of three dimensional pattern analysis, by the comparison of parallel human and computer EKG diagnostic efforts, and by a study of the advisability and possibility of introducing major, tree-like branching decisions early in the diagnostic process.

Staten, S.F. and Stark, L.: A Statistical Analysis of Pupil Noise. *IEEE Trans. Biomed. Engin., 13:3, July 1966.*

The random fluctuations of human pupillary area provide an interesting example of a stochastic process in a biological system. Statistical theory and system analysis have guided the authors in performing experiments which reveal important properties involved in the random process.

The purpose of this paper is to present the various experiments performed during this investigation and to propose a system model which not only describes the average pupil response to a given stimulus but also the random fluctuations called pupil noise. We classify these fluctuations as noise in the sense that noise usually connotes a signal which does not seem to serve any useful purpose.

No attempt will be made here to describe the pupil physiology or to present the mathematical foundations of the statistical theory. The reader is referred to the references at the end of the paper for this background information.

Taylor, S.G., III: Abstract of Editorial "Cancer and the Internist." *Ann. Intern. Med., 65:1, 189-91, July 1966.*

With the internist's knowledge in diagnosis, hematology, endocrinology, cardiology, respiratory disease, gastroenterology, neurology, and pharmacology, his contribution to the total care of the patient with cancer should be at least as great as that of the radiotherapist and surgeon. He should, in fact, be responsible for all phases of cancer from primary diagnosis to the terminal care of the patient.

It is interesting that in the most recent pamphlet on the "Essentials of Approved Residency" there is no mention of a training program in oncology in the medical residency program. Because of the dearth of questions related to cancer appearing in the examinations of the American Board of Internal Medicine, residents in medicine are apt to neglect opportunities for experience in this field during their training. Contributions in the field of cancer in departments of medicine will, undoubtedly, be of greater and greater value if all phases of the disease are adequately emphasized in training programs for medical residents.

Physicians of many different specialties are called upon to give therapy in the various stages of cancer. A too-frequent result is that there are many doctors involved, but no one managing the problems of the patient in totality. The internist can best take this unfilled role and may thereby serve the patient as the one man who is specifically interested in him.

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VOL. 6 NO. 2 APRIL 1967

BIOMEDICAL ENGINEERING

Accommodative Convergence

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Sampling of Intermittency in the Hand Control System

The Editor's Page

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ACCOMMODATIVE CONVERGENCE:
An Adaptive Nonlinear Control System

JERALD BRODKEY, M.D.[1]
LAWRENCE STARK, M.D.[2]

INTRODUCTION

The interest accorded to the lens system of the eye matches its importance as a major element in a principal pathway of perception. The surgical removal of cataracts is one of the oldest of operations and the study of physiological optics has had a long history. However only recently have techniques, both instrumental[1] and mathematical,[2] become available to allow a dynamic analysis of the accommodation system. The accommodation of the visual system to distance actually involves much more than a mere change in the diopter power of the lens, but includes changes in pupillary size as well as in the degree of convergence of the eyes. These latter two functions are controlled by reflex mechanisms at a subconscious level. The experiments described here are concerned with convergence of the eyes during accommodation for distance, i.e. accommodative convergence, as illustrated in Figure 1. Accommodative convergence is not only of interest as a system in its own right, but also gives clues about the dynamic characteristics of the lens system as well. Our experimental technique and results will be described first, after which we will attempt to relate this work to the efforts of other investigators in the field.

PROCEDURE

A target, consisting of a fiber optic one millimeter in diameter mounted on an X-Y recorder, lay in the visual axis of the right eye. A six diopter lens was placed between the right eye and the target so that the eye was at one focal point of the lens and the target was closer to the lens than the other focal point. In this manner, a virtual image of the target was formed with the following advantages. Relatively large changes of target position in diopters could be accomplished with small movements of the target on the X-Y recorder. Secondly, a linear relationship exists between the actual distance of the target along the X-Y recorder and the distance in diopters between the virtual image and the eye.

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The authors would like to acknowledge the support which Dr. Brodkey received as an NIH Special Fellow for the year 1965-66 as well as the encouragement of Dr. William Sweet

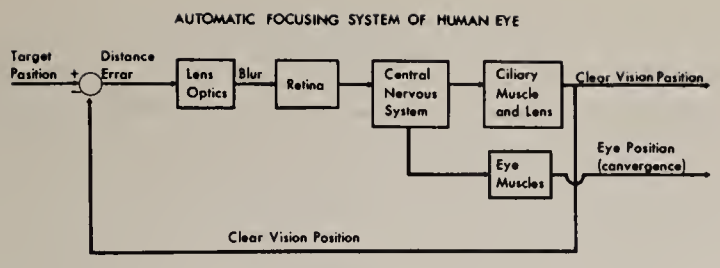

Fig. 1.—Automatic Focusing System of Human Eye.

In this way, target distance in diopters was a linear function of the voltage signal driving the X-Y recorder. Finally, the apparent size of the target remained constant whatever its distance from the eye so that the size of the target was no longer a clue as to its distance from the subject's eye.

The left eye was not allowed to visualize the target, but its movements were monitored and thus permitted a measure of the degree of convergence of the eyes.[9] The monitoring system consisted of two photo-sensitive diodes mounted in front of the left eye and forming two arms of a bridge circuit, as previously described.[3] The target movement as well as the left eye movement were recorded on a penwriter, as shown in Figures 2 and 3, and could be further processed with a bank of operational amplifiers. Furthermore, a medium-sized digital computer (GE-225) was available for use in an "on-line" fashion to generate target movements as well as to analyze the resulting convergence movements.

SINUSOIDAL TRACKING

Single Sinusoids

The response to sinusoidal target movement in the optical axis of one eye, as described above, is a movement of the contralateral eye, in association with the lens accommodative respect, which closely approximates a sinusoid of the same fundamental frequency as the input. A typical record is shown in Figure 2. The lower trace is a record of the target movement, which in this case was a sinusoid of 0.8 cps and 2 $\pm$ 0.5 diopters amplitude. The upper trace is the record of the resulting eye movement and it is apparent that there is both phase lag and gain modulation present. A single sinusoidal analysis of the system was performed by making short runs at single frequencies and two amplitudes of target movement, as illustrated in Figure 3. In all, eight frequencies ranging from 0.2 to 2.5 cps were used with three sizes of target movements: 2 $\pm$ 0.3, 2 $\pm$ 0.5, and 2 $\pm$ 0.8, diopters. The combined data of numerous runs is illustrated in Figure 4.

While the data clearly shows a different attenuation in gain for each size ampli-

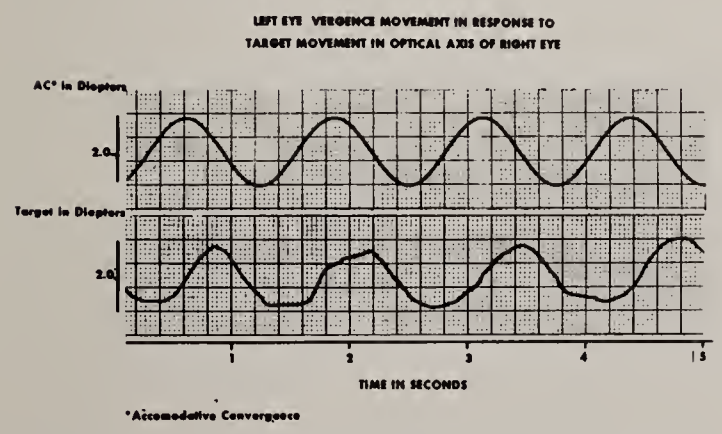

Fig. 2.—Left eye vergence movement in response to target.

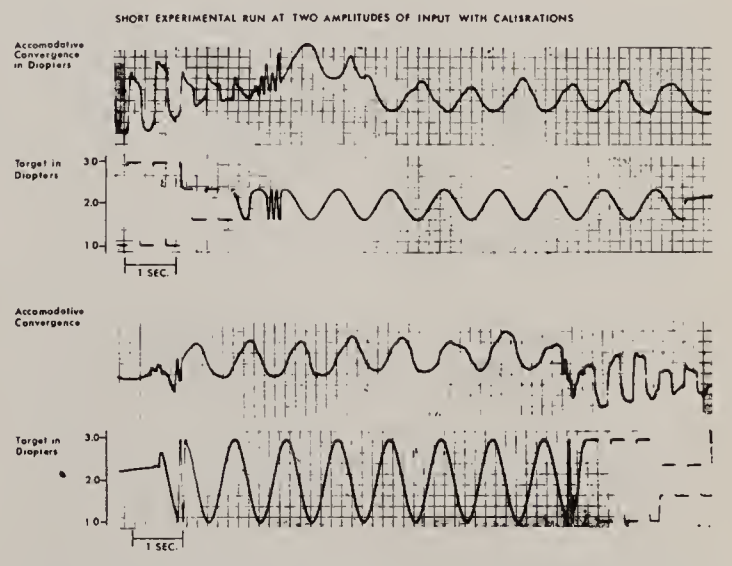

Fig. 3.—Short experimental run at 1.0 cps and two amplitudes of input with calibrations.

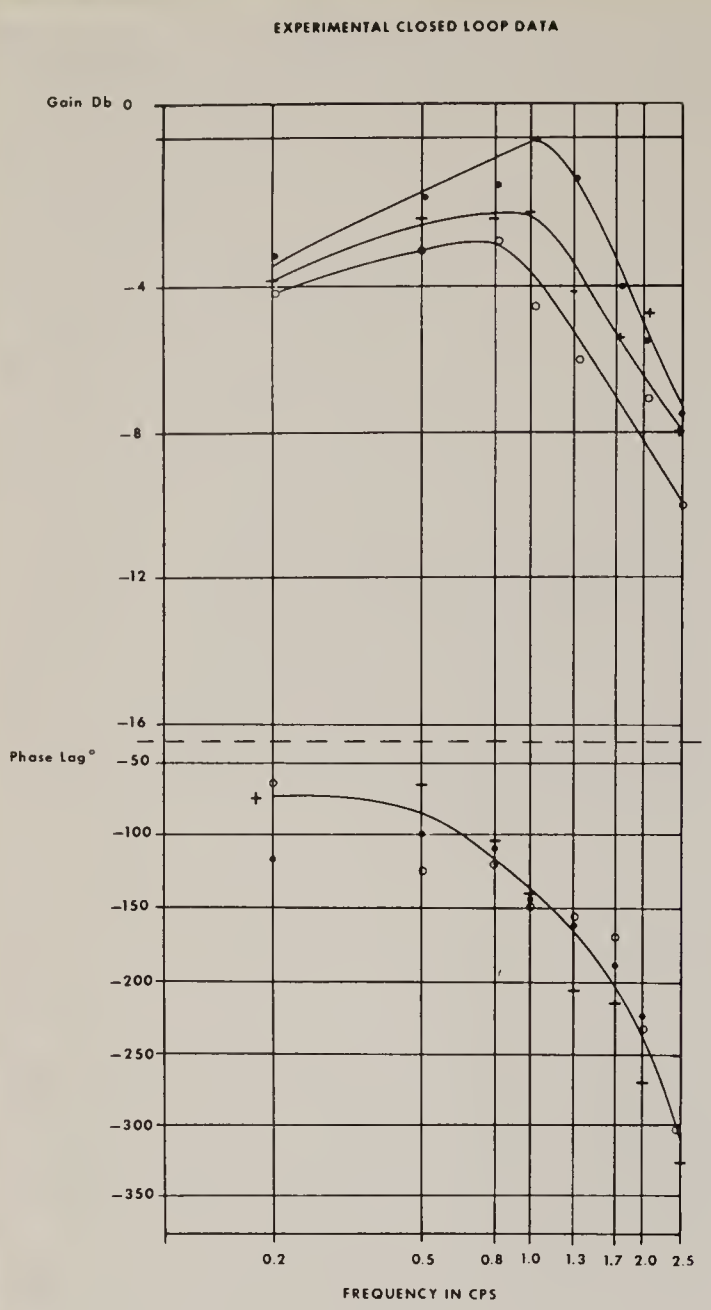

Fig. 4.—Experimental closed loop data.

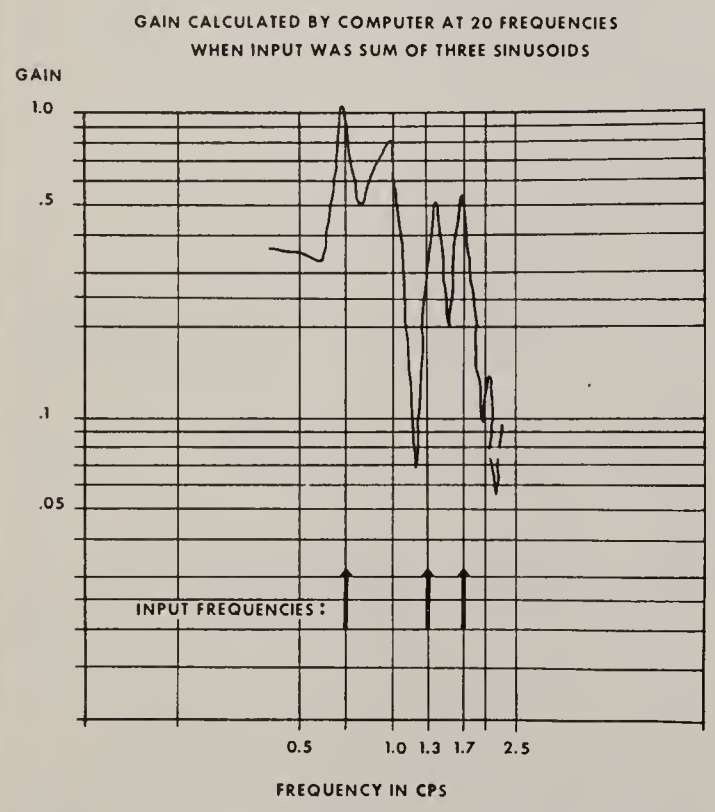

Fig. 5.—Gain calculated by computer at 20 frequencies when input was sum of three sinusoids.

tude of input, the phase lags for the different sized amplitude inputs seem to be almost the same. As the target movement amplitude increases, the gain of the system falls off. The significance of this nonlinearity will be further discussed when the system is modeled as containing a no-memory nonlinearity.

Multiple Sinusoids

The response of the system to inputs consisting of the sums of sinusoids of the same amplitudes but differing frequencies was also studied. Two different types of experiments were done. In the first type, three sine wave oscillators were used to generate a target movement and the digital computer was used "on line" to perform a Fourier analysis of the resulting eye movements. Thirty seconds of data was taken for each run with 100 data points per second. Figure 5 shows the calculated results from a typical experiment. In this case, the input signal consisted of a sum of equally sized sinusoids of 0.7, 1.3, and 1.7 cps with a total target excursion of 2.6 ± 0.6 diopters.

From data of this sort showing peaks in the gain curve at those frequencies which formed the input signal, again the conclusion was drawn that the output of the system when driven by a sum of sinusoids could be approximated by a sum of sinusoids of those same frequencies that were present in the input signal.

The second type of experiment consisted of using the computer to generate a target motion consisting of four sinusoids at specified frequencies and to analyze the resulting eye movement at those same frequencies for both gain and phase lag. These experiments were all performed using input target amplitudes of 3 ± 1.0 diopters and various frequencies between 0.2 and 1.3 cps. Figure 6 shows the combined data from many individual experiments. The gain data has been considerably more variable than the phase data and much more work of this type needs to be done. The phase lags for both the single and multiple sinusoidal target movements are quite

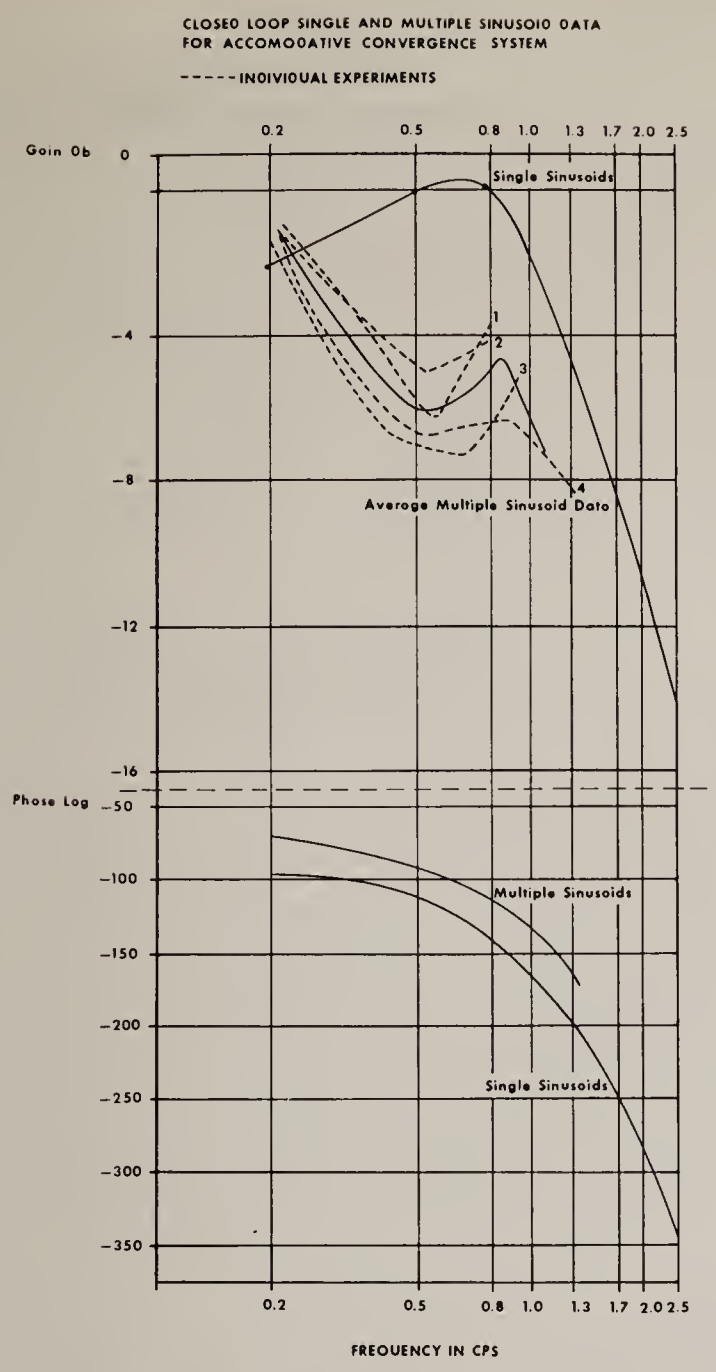

Fig. 6.—Experimental closed loop data. When input was a sum of 4 sinusoids. Lower gain but smaller pulse was found lag as compared with response to single inputs.

comparable but the multiple sinusoidal data has a phase lag 25° less than that of the single sinusoidal data. The gain curves are more attenuated than those for the single sinusoids.

Instability Oscillations

During the course of the sinusoidal tracking experiments described above, it was found that the accommodative system was only marginally stable and could be easily provoked into a condition of sustained oscillation. Two different means could be used to provoke this oscillation. Either the target amplitude could be diminished below 2 ± 0.2 diopters, or the frequency of oscillation of the target could be lowered to a region below 0.2 cps. An example of the latter case is illustrated in Figure 7.

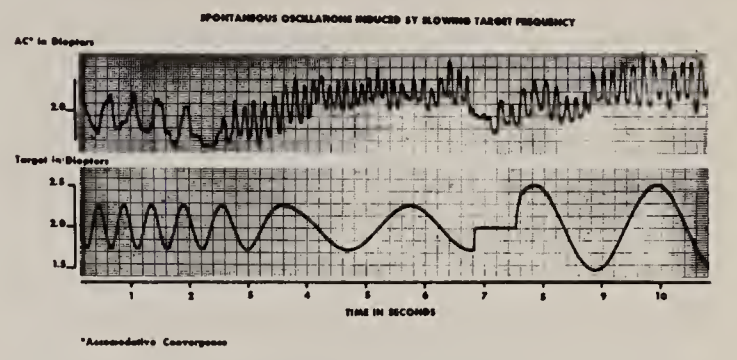

Fig. 7.—Spontaneous oscillations induced by slowing target frequency.

Here oscillations were produced when the target had slowed to about 0.25 cps. Characteristically they were 1.3 cps and about ± 0.4 diopters in amplitude. It is interesting that one subject recognized that the target stopped and stopped his oscillating movement but again started the oscillatory behavior when the target again began its slow movement. Referring to Figure 11, one can see that these oscillations are really oscillations produced in the closed loop of the accommodative system and only recorded through the accommodative convergence system.

OPEN LOOP EXPERIMENTS

In an effort to determine the open loop characteristics of the system, experiments were performed in which the loop was physiologically opened. This procedure was accomplished as illustrated in Figure 8. If it is assumed that the physiological feedback has a gain of 1, and that the eye position is strictly proportional to the diopter power of the lens, then it should be possible to feed back the eye position signal through a variable gain amplifier and thus control target position. In this manner one could cancel the physiological feedback and study the system in

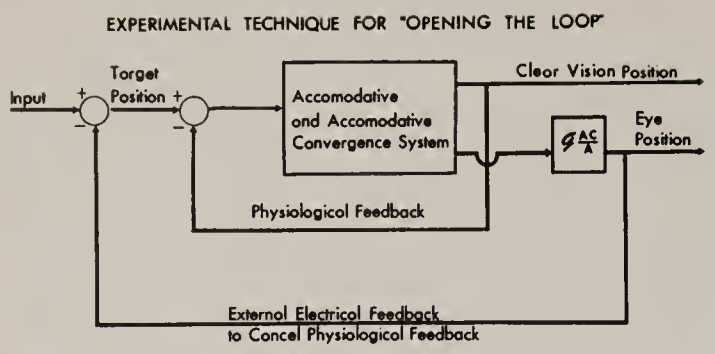

Fig. 8.—Experimental technique for "opening the loop."

its open loop state. Such experiments were done and examples are shown in Figure 9. Evidence in favor of the correctness of these assumptions is presented in the Bode diagram of Figure 10 where experimental open loop gain and phase results are compared to open loop gain and phase plots derived by calculation from the closed loop data.

Subject Experience and Variability

Finally it should be added that subject experience and experimental technique are crucial factors in obtaining the above data. To obtain consistant data it was found necessary to perform experiments first thing in the morning and to avoid tiring the subject. The data for the Bode plots was obtained over a number of days. Even the consistency of short runs had to be constantly checked; and it was found that often the calibration following a run with the faster frequencies would be lower than the initial calibration as demonstrated in Figure 3 and this data had to be discarded. An often noted phenomenon was the tendency during a run for the operating DC level of the system to shift slightly toward increased convergence, but this did not seem to affect the gain and phase data. Subject characteristics are most important. One experienced subject, A.T., was not used for these experiments because he could predict the sinusoidal target movement and could follow sinusoids of all frequencies with either no phase lag or a slight phase advance. He could also be driven into instability oscillations by reducing the target movement amplitude during a run, but the oscillations would

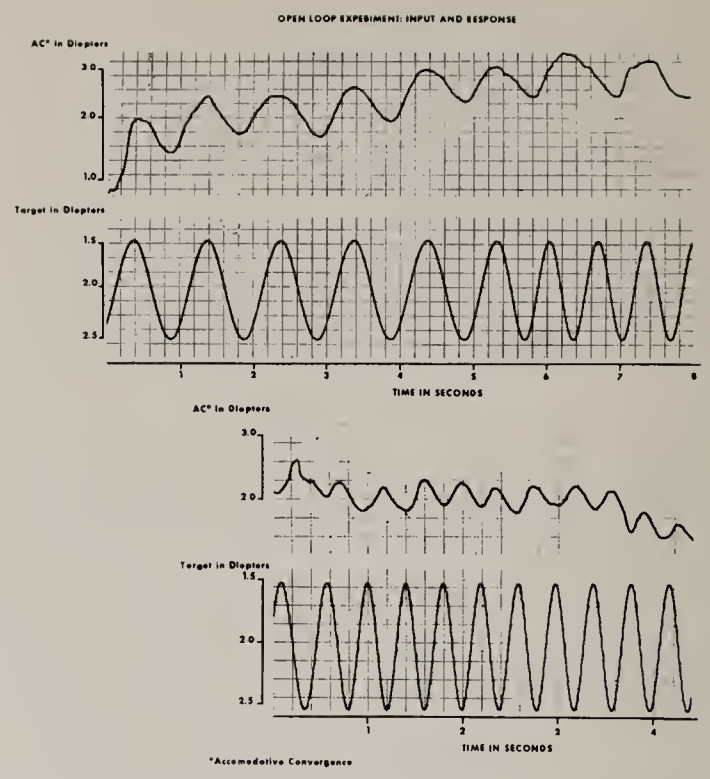

Fig. 9.—Open loop experiment.

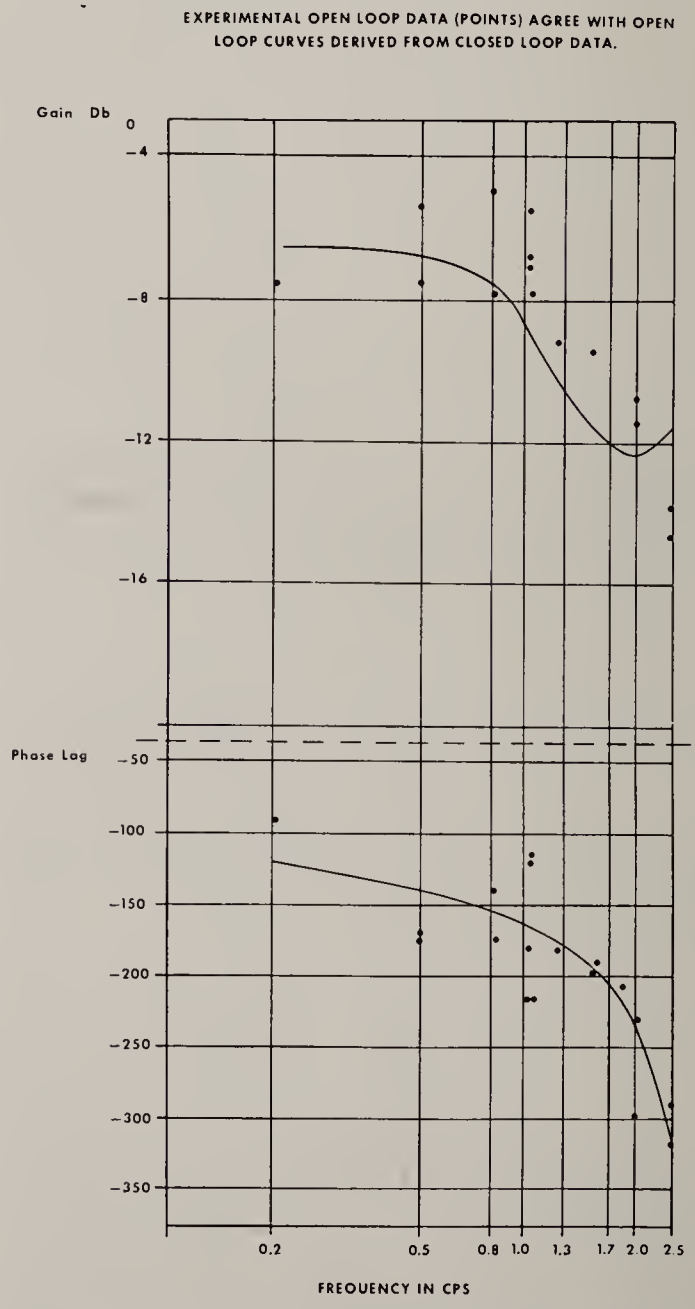
EXPERIMENTAL OPEN LOOP DATA (POINTS) AGREE WITH OPEN LOOP CURVES DERIVED FROM CLOSED LOOP DATA.
Gain Db
Phase Lag
FREQUENCY IN CPS

Fig. 10.—Experimental open loop data (points) agree with open loop curves derived from closed loop data.

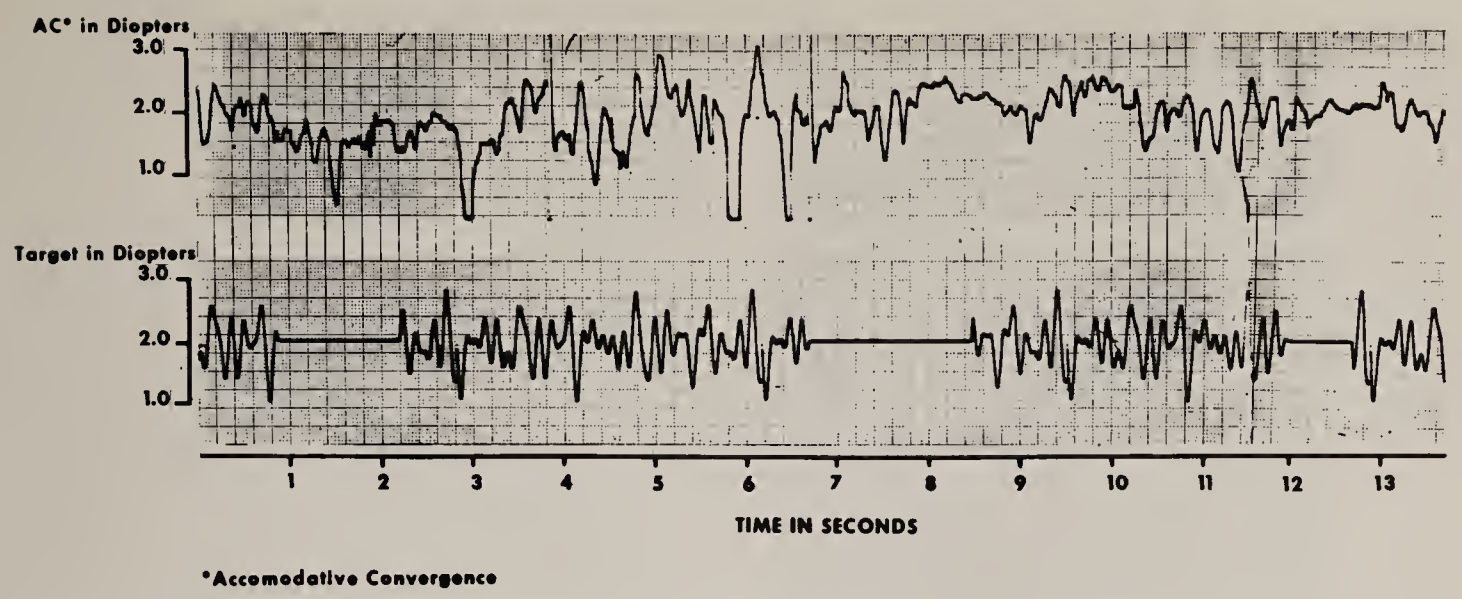

Fig. 11.—Oscillations occurring when target was stationary.

die out in four or five seconds. In other words, referring to Figure 11, while the first subject, J.T., could not distinguish between that portion of the distance error which was due to fluctuations of target position from that due to fluctuations of clear vision position, the second subject could make this distinction after several seconds of spontaneous oscillation. On questioning, it was found that his modus operandi in the latter case was to note changes of target shape caused by his own astigmatism operating on fluctuations of clear vision position. Because of the difficulty of obtaining cooperative subjects most of the experiments were performed on only two subjects, and some indeed on only one.

SAMPLING

A number of biological systems have been found to behave as if they were sampled data systems. These systems include hand tracking as well as the saccadic portion of the eye tracking system. Functionally, such a system behaves as if it were not operating on data flow continuously but rather at discrete time intervals. Figure 13 shows the results obtained when a short pulse is delivered to the horizontal eye tracking system, the eye following with saccades. As illustrated, following the initial target movement a saccade is produced with the characteristic reaction time or delay. However, another saccade is not produced almost immediately with only the target width delay so that the eye does not follow the short pulse of the target with an equally short pulse only delayed by a reaction time. Conversely, the system waits approximately 0.2 seconds before another saccade is produced.

When similar experiments are performed using the accommodative convergence system, a different result is obtained which leads to the conclusion that the system does not operate in a sampled data fashion. Figure 14 shows the responses to a long and a short pulse.

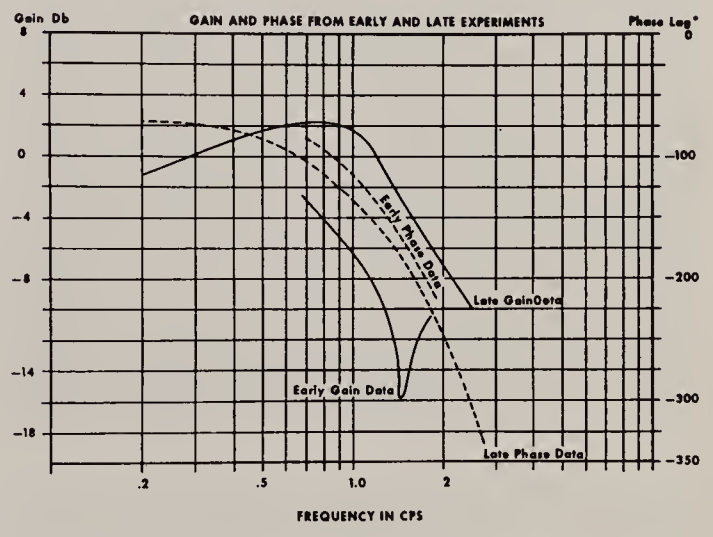

Fig. 12.—Effect of subject's experience.

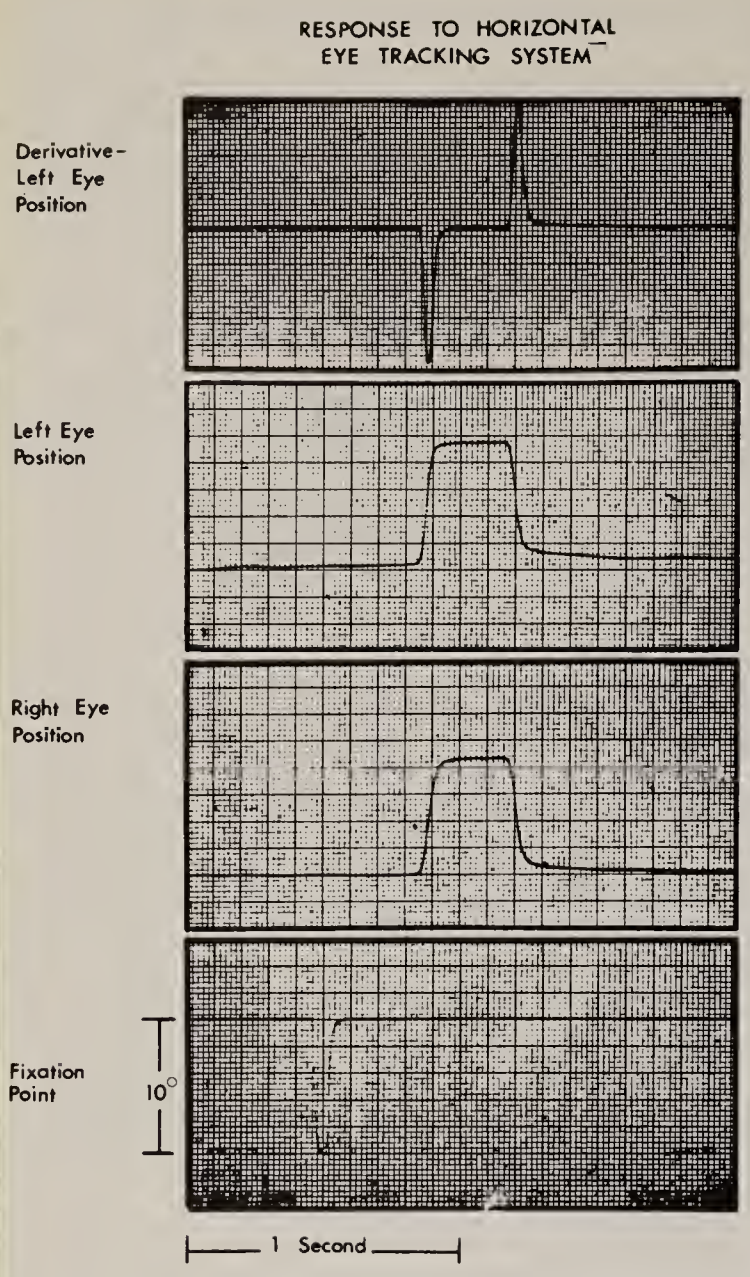

Fig. 13.—Response of horizontal eye tracking system.

The target in each case was moving toward the subject and his reponse was a short term, small increase in degree of convergence. The single responses in this experiment are more difficult to interpret than those of the saccadic system in horizontal eye tracking because in this system the dynamic characteristics of the response are so slow that the response to the initial leg of the short input pulse is not yet complete before the occurrence of the final leg of the short input pulse.

The question can be resolved however, if one looks carefully at the two responses, and this is best done if one looks at their difference as illustrated. Here it is apparent that at a point which is equal to the sum of the reaction time of the system plus the duration of the short pulse, the two responses begin to diverge. In other words, even though the responses to the pulses are far from complete at so short a time interval, one can still demonstrate the difference in control policy being exerted on the response within 90 milliseconds after the beginning of a response.

Figure 14 shows averages produced by the computer of several responses, while Figure 15 shows individual responses of typical or modal nature from the same experiment saved on magnetic tape and later subtracted by the computer.

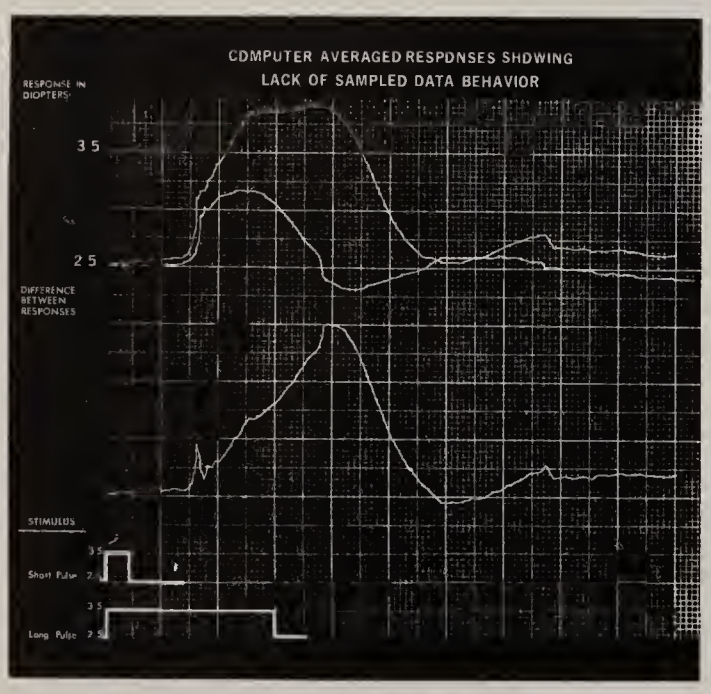

Fig. 14.—Computer averaged responses showing lack of sampled data behavior.

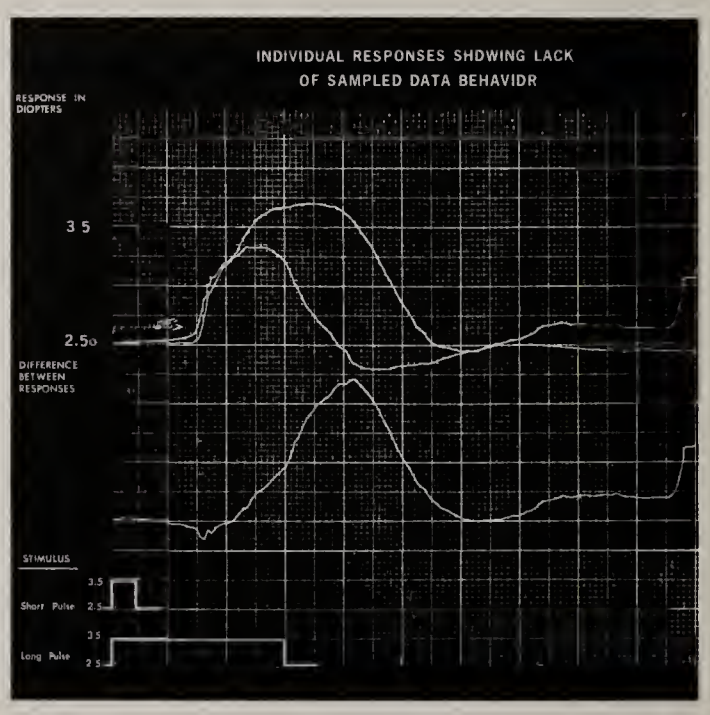

Fig. 15.—Individual responses showing lack of sampled data behavior.

In an effort to further understand the significance and interrelations of the above data, an attempt has been made to construct a mathematical model. The gain and phase data as illustrated in Figure 4 show different gain curves but basically the same phase lags for various size inputs thereby leading to a model of the system containing a no-memory nonlinearity combined with a linear element. Such a system would appear as in Figure 16.

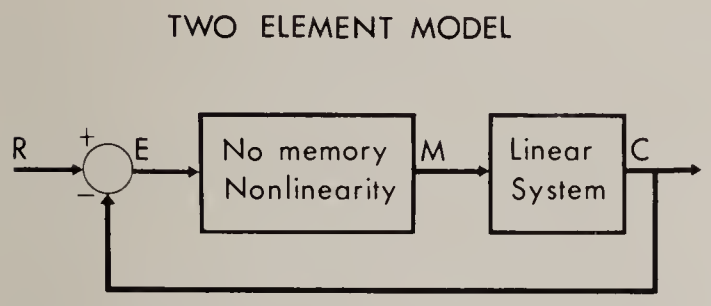

Fig. 16.—Two element model.

The first step in constructing the model was to calculate an open loop Bode plot using the experimentally measured closed loop curves. The calculation was performed graphically using a Nichols chart[14] and the results are illustrated in Figure 17. Noting that

$$|E(jw)| = |R(jw)| \cdot |C(jw) \div R(jw)| \cdot |E(jw) \div C(jw)| \quad (1)$$

It was possible to calculate the absolute value of the error for each frequency and size of input. The results of this calculation are presented in Figure 18. If the open loop gain is then plotted as a function of the error for each frequency and size of target movement, Figure 19 is obtained. The fact that the line segments for each frequency in Figure 19 have negative slope is of course indicative of the nonlinearity of the system.

If the system could be modeled in the form of Figure 16, then the line segments of Figure 19 should be parallel to the extent that they traverse the same region of error. They are not parallel and consequently a model in the form of Figure 20 was chosen. For reasons that will be discussed later, $F(s)$ was taken to be a differentiator, ie $F(s) = s$. One can then plot $|C/E|$ as a function of $|\dot{E}| = |sE|$ as shown in Figure 21. These line segments are now quite parallel and could well be segments of a describing function of the nonlinear element of Figure 20.

If they are, then they can be moved vertically by an amount given by the gain of all of the linear frequency-dependent elements. Thus one is led to a describing function as illustrated in Figure 22.

One can then easily calculate the total linear open loop transfer function and

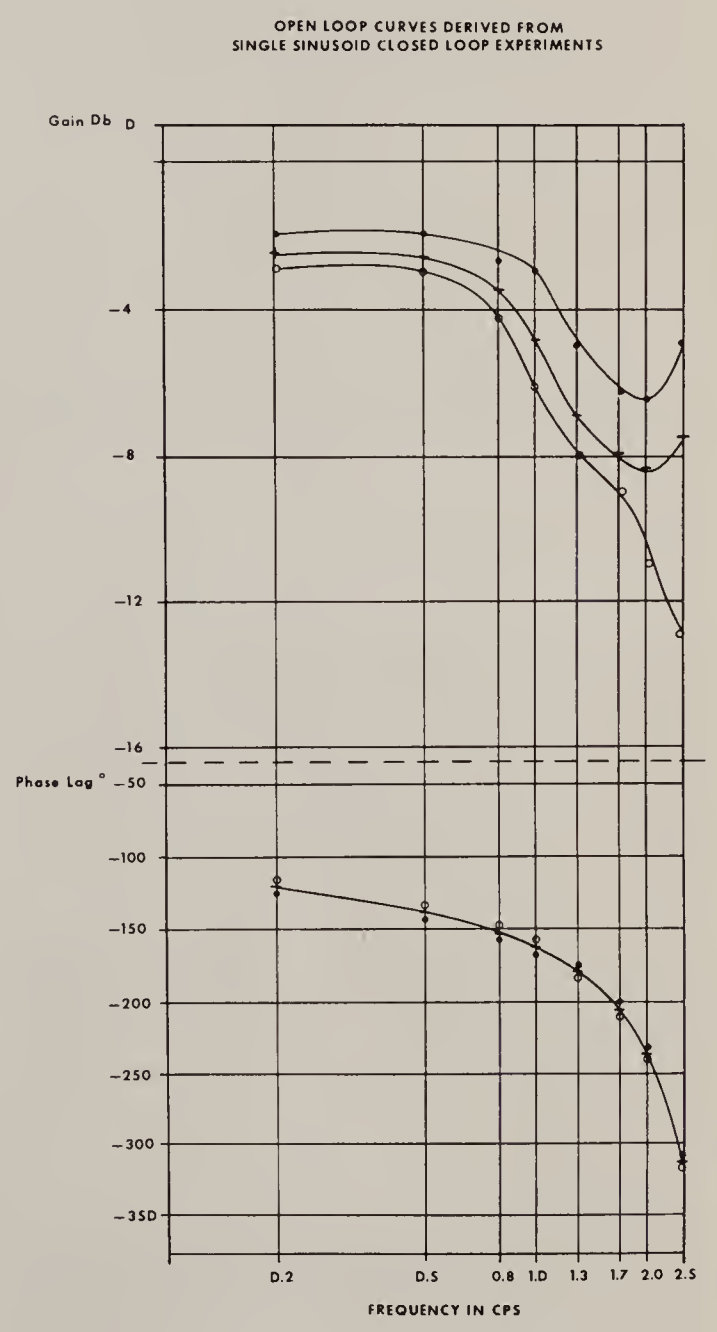

Fig. 17.—Open loop curves derived from single sinusoid closed loop experiments.

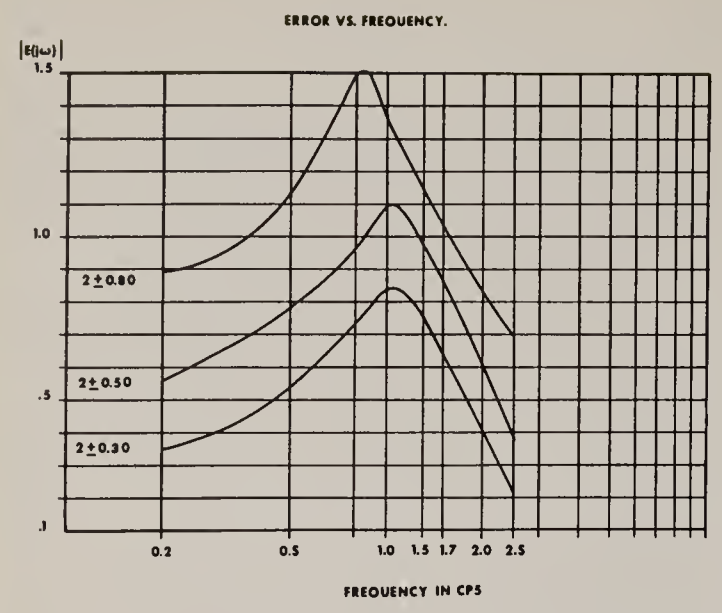

Fig. 18.—Error vs. Frequency.

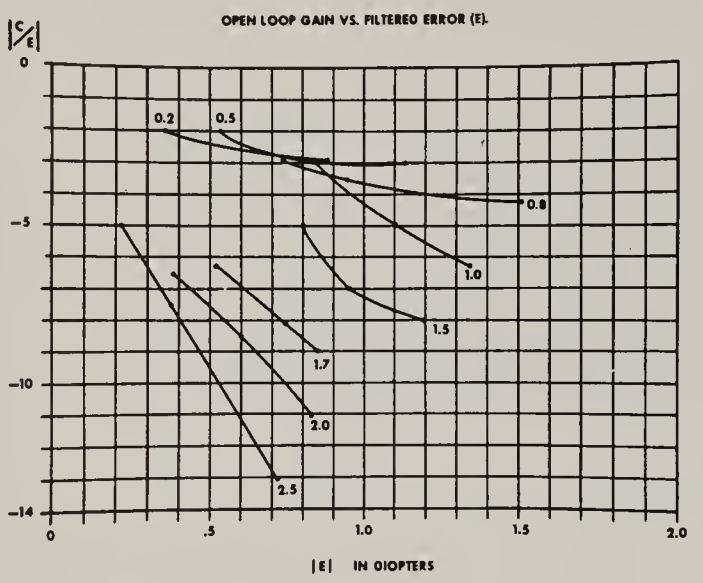

Fig. 19.—Loop gain vs. error.

that portion of it, $G(s)$, that follows the nonlinearity. These gains are given in Figures 23 and 24. Consequently, one is led to the model as illustrated in Figure 25; the factor $e^{-0.3s}$ is the non-minimum phase element derived from the phase data. However, from Figure 26 it is apparent that the phase predicted by this model leads the actual data by 90° at low frequencies and lags the actual data by 90° at high frequencies. The

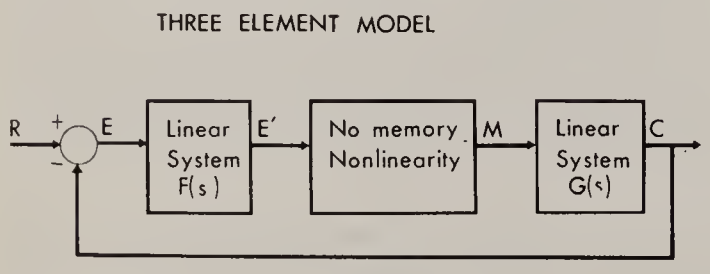

Fig. 20.—Three element model.

phase data is best described by a linear element of the form $e^{-0.3s}\ (1+0.18s)/(0.18s)$.

In a further attempt to find a consistent model for the gain and phase data, a model of the form of Figure 27 was used. If the system is of this form, and if $H(s)$ is chosen as

$$H(s) = e^{-0.3s}(1 + 0.18s)/(0.18s) \quad (2)$$

then C/E should have no phase lag but a gain characteristic given by Figure 28. The plot of $|C/E|$ as a function of $|E|$ is given by Figure 29. Simple calculation then shows

$$F(s) = (1 + 0.18s)^4/(0.18s)^2 \quad (3)$$

and

$$G(s) = (0.18s)^2/(1 + 0.18s)^4 \quad (4)$$

The describing function for the nonlinear element is given in Figure 30, and the whole model in Figure 31.

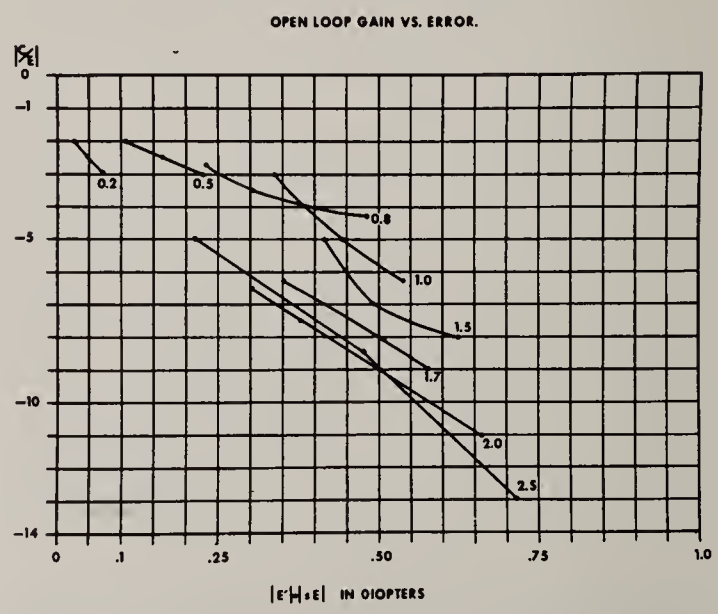

Fig. 21.—Open loop gain vs. filtered error (E).

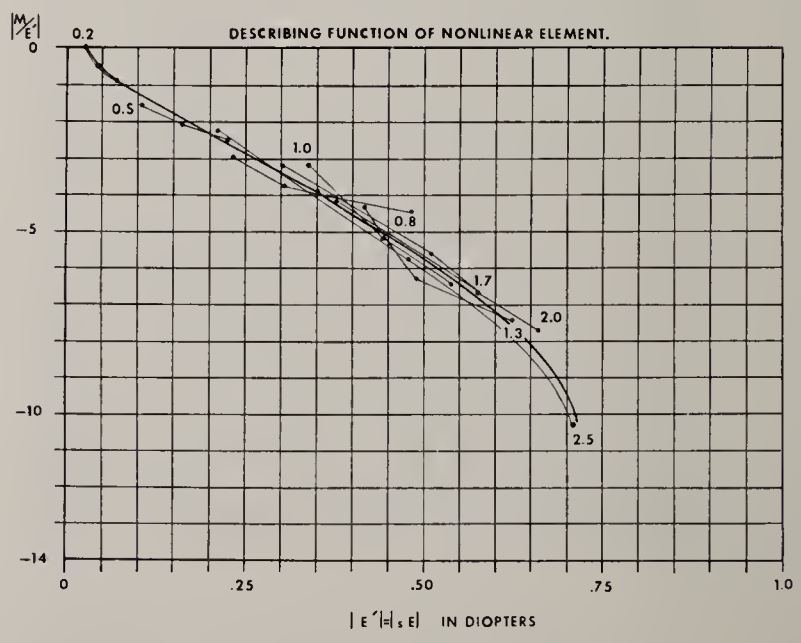

Fig. 22.—Describing function of nonlinear element.

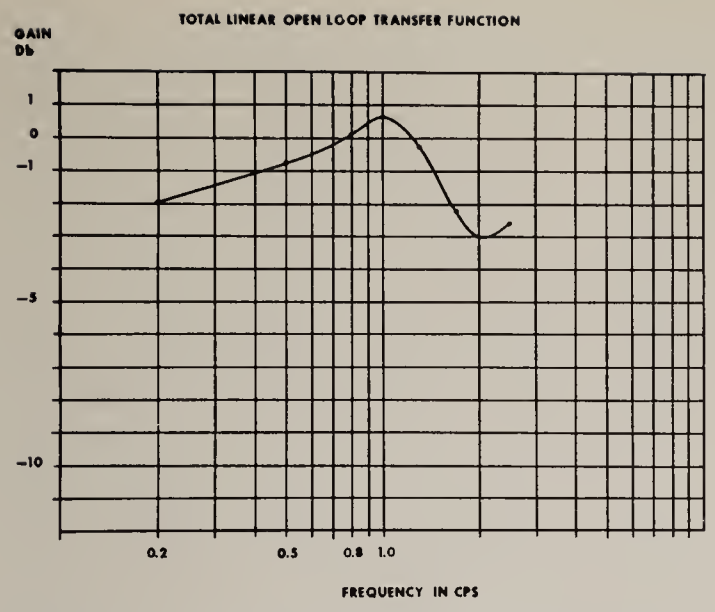

Fig. 23.—Total open loop linear transfer function.

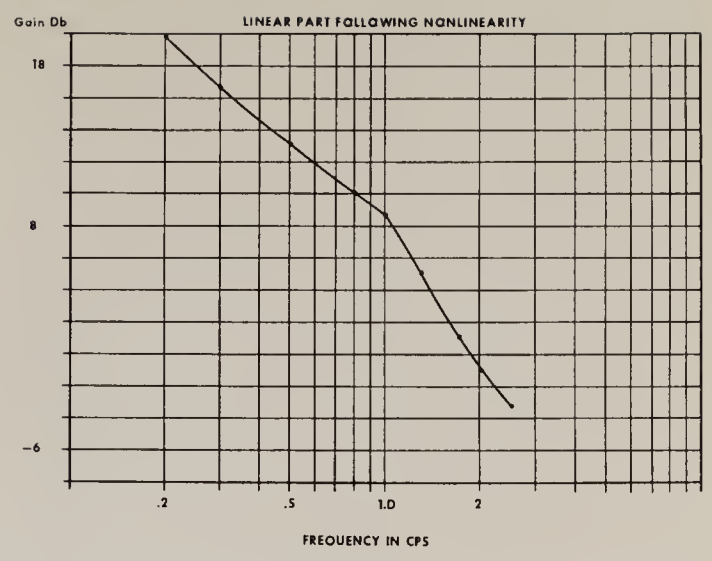

Fig. 24.—Linear transfer function of output element. Final linear element.

DISCUSSION

Many studies of the relationship of accommodation to accommodative convergence have been performed,[14,15,16,17] and the ratio (Ac/A) of the one to the other described. Since our experimental technique does not at present allow us to measure this dynamically, we have had to content ourselves with a static measurement (1/2) under our experimental conditions and make the assumption that it is stationary. How closely the actual system approximates this ideal will have to be investigated further, but we are encouraged that it is approximately free of dynamics by the following consideration. The open loop phase as calculated from closed loop data and as measured experimentally would imply that the system, if it did oscillate would oscillate at 1.3 cps—which it does. If the ratio (Ac/A) was frequency dependent, the open loop data would probably have predicted a different oscillation frequency.

The question as to whether or not the accommodative system operates in a sampled data fashion has never been adequately resolved. On the one hand, there is the obsérvation[4] that during slow sinusoidal tracking, step discontinuities in accommodation are evident.

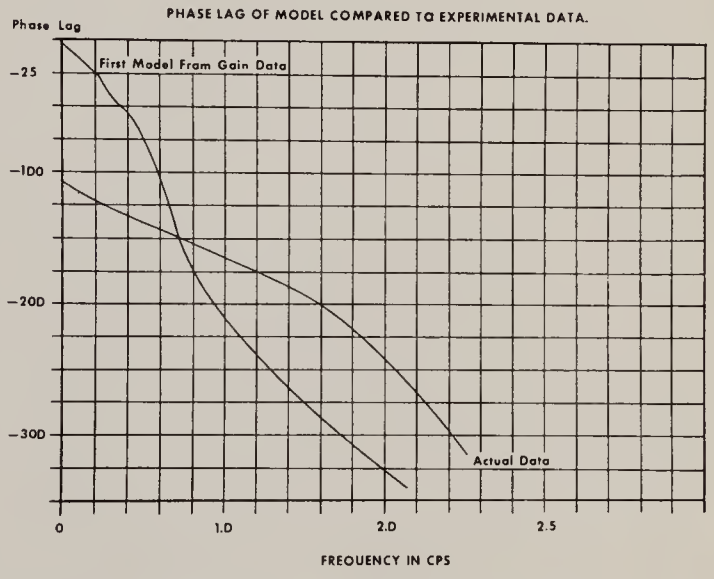

Fig. 26.—Phase lag of model compared to experimental data.

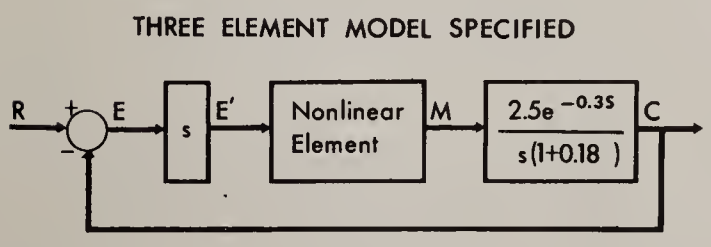

Fig. 25.—Three element model specified.

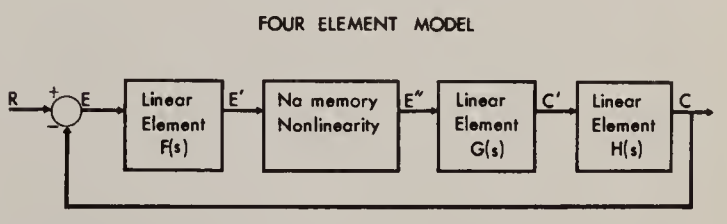

Fig. 27.—Four element model.

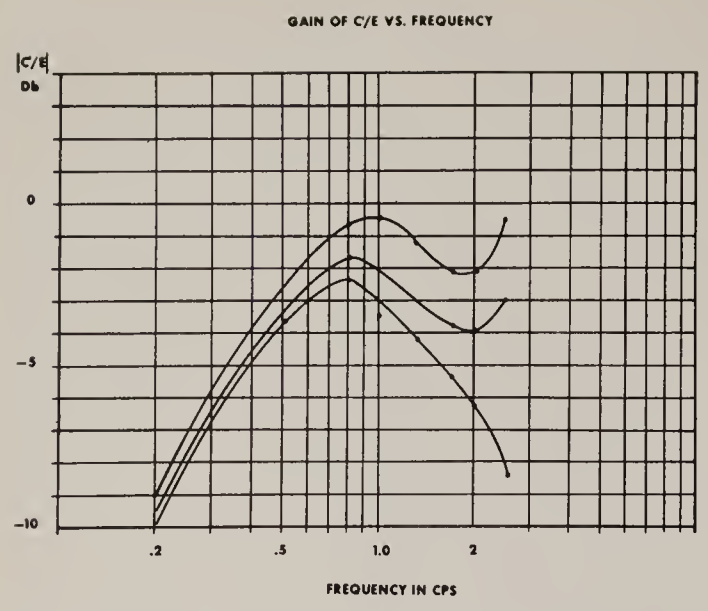

Fig. 28.—Gain of C/E vs. frequency.

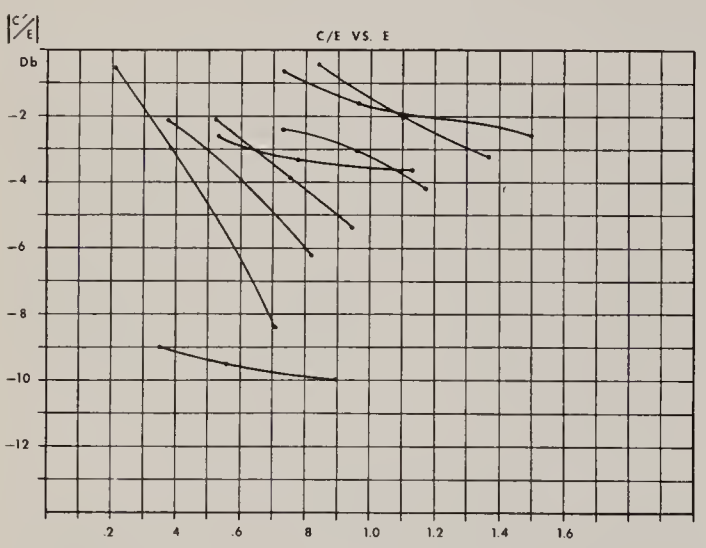

Fig. 29.—$|C'/E|$ vs. $|E|$.

We have also noted the same phenomenon in our data. Furthermore, the well known 2 cps peak[5] in the power density spectrum of the accommodation system has been likened to the corresponding peak in the gain portion of the Bode plot of the horizontal eye tracking system[6,7] whose saccadic portion is thought to operate in a sampled manner.[6,7,8] Also, figures in a paper on trial and error in accommodative tracking[9] clearly show that when the accommodative system responds to a step input in the wrong direction, there is considerable delay (0.3 to 0.6 sec.) before the error is corrected.

On the other hand, Campbell and Westheimer[4] have shown that responses to pulse stimuli can be modified even during the actual course of the response.

The crucial question which we undertook to answer was exactly how soon after its beginning the response can be modified, and whether this time interval depends only on the pulse being presented or whether it is modulated by other factors in the system. The results shown here seem to indicate that the accommodation system is quite capable of modifying its behavior depending upon the target motion. In other words, the system does not behave in a sampled data fashion. However, because of the dynamics of the system this modification is hard to detect in its early stages. An explanation for the relatively long time interval before the output errors in the system are corrected is simply that an error in the output behavior could not possibly be corrected prior to one reaction time following the onset of the output.

The sinusoidal tracking data obtained for the accommodative convergence system is in many respects similar to that obtained from the accommodative system itself.[5,2] The same type of no-memory nonlinearity[2] seems to be present. With smaller target movement amplitudes the

Fig. 30.—Describing function of nonlinear element of four element model.

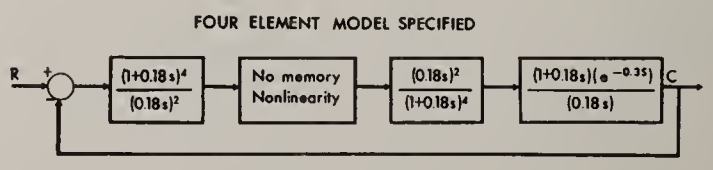

Fig. 31.—Four element model specified.

gains are higher, but phase does not seem to be greatly modified by variations in target movement amplitude. However, the gain portion of the accommodative convergence Bode plots shows a peak at one cps while that of the accommodation alone peaks at two cps; similarly, the phase curves of the former system show greater phase lag for each frequency than does the latter system. Whether these discrepancies represent only a difference in the subjects used, or a true difference between the two systems remains to be seen. A dynamic optometer is now under construction in our laboratory and we hope to have the answer in due course. The problem which arises is the interpretation of the 1.3 cps oscillations illustrated above. Are these basically the same as those 2 cps oscillations investigated by Campbell[5,10] or do they represent a truly different phenomenon? Although the more rapid oscillations do not seem to be a prominent feature of our records, even from the illustrations shown here one might deduce that they are present. Furthermore, the 1.3 cps oscillations are much more regular and considerably larger (± 0.4 *D*) than 2 cps oscillations. Even so, it is noteworthy that the open loop phase data here implies 1.3 cps oscillations. Further data will have to be collected before one will be able to decide whether this discrepancy in frequencies is due to different subjects, to different operating conditions, or to a different system being measured.

The adaptive nature of this system is quite interesting. In spite of reflex dependence of accommodative convergence on lens accommodation, the entire system is under voluntary control and seems able to change its operating characteristics under various circumstances. These changing characteristics make the experimenters job more difficult as explained above under subject variability. Just as the hand tracking system[11] and the horizontal eye tracking system[12] show evidence of a prediction operator or signal input adaption, the results here for accommodative convergence show evidence of it as well. These results are illustrated in Figure 6. It is interesting that these same features are present in Figure 12 comparing the early and late records from the same subject. Presumably his abilities to predict target motion would be less well developed early than late in the course of training. As distinct from the other two systems mentioned above, here there was a phase advance rather than a retardation for the unpredictable inputs. Whether this finding will be true for other subjects will be checked in the future.

As illustrated in the records above, the behavior of the system during spontaneous oscillations shows further evidence of adaptive behavior. This is particularly true of the record of Figure 11 during which the distance error, as determined by the clear vision position, was tracked (even though target position was constant) until the subject (A.T.) noticed his astigmatic error, changed his mode of behavior, and stopped oscillating.

The two models as represented in Figures 25 and 31 are an effort to compress the various graphs and curves of this data into a more manageable form. The first model has the advantage of simplicity, but it does not adequately represent the phase data. This discrepancy seems quite serious to us because in general, the phase data has probably been more consistent from run to run than the gain data. The phase data also seems to accurately predict the system's time delay experimentally determined by transient studies in the time domain. The choice of a differentiator as a first element seems quite reasonable. One might surmise that the movement of the image blur across the retina is a greater stimulus to accommodation than a more stationary image. If this fact were true, it might well explain the well known difficulties encountered in following very slowly moving accommodative targets. The form of the second more complicated model does not preclude the initial retinal operator from being a type of differentiator. In general, one might divide the open loop system into a fre-

quency dependent error sensing device of which the retina is a part, an error correcting element of which the nonlinearity is probably a portion, and the final plant. In this format, it is interesting to speculate that those experimental situations producing difficulty in and instability of accommodation might all be associated with small signals being produced by the error sensing element: 1) progressive reduction in the frequency of the sinusoidally moving target leading first to discontinuous changes in accommodation and later to oscillations as illustrated in Figure 7, 2) progressive reduction in the amplitude of sinusoidal movement leading to a slower traversal time of bluredge across the retina (probably fovea), 3) reduction of target illumination,[13] and 4) size of target.[18]

It is suggested that one type of adaptive function is to vary the gain of the controller or error correcting portion of the system, and hence the total open loop gain. The open loop gain, both as measured directly and calculated from the closed loop data is never 1. Hence it might be argued that the system could not go into spontaneous oscillations. However, if the gain of the controller were varied to compensate for the size of the signals produced by the error sensing portion of the system, then one might expect all of those situations listed above leading to small output of the error sensing element to increase the open loop gain and drive the system to instability. This formulation would agree with the finding of Campbell Westheimer and Robson[10] "the slower components" of lens fluctuations "appear to increase in amplitude when the dead space is increased by diminishing the pupil size or by presenting the subject with an empty visual field." Needless to say, more experimental work is needed to verify these hypotheses.

SUMMARY

Accommodative convergence of the eyes relates to reflex convergence when the lens accommodates for distance. The system has been studied in both frequency and time domains by providing sinusoidal and pulse stimuli of target distance from the eye and measuring the degree of convergence as output.

Both predictable single sinusoidal and nonpredictable multiple sinusoidal data are obtained and related to subject experience in tracking. The results for single sinusoidal input at varying input amplitudes show the system to behave as if it contained a no-memory nonlinearity. Open loop single sinusoidal data was measured directly and compared with open loop Bode plots theoretically derived from the closed loop data. Instability oscillations are demonstrated and their frequency is predicted by the open loop data. A mathematical model to describe the data is derived.

The adaptive nature of the system is discussed and evidence is given for a prediction operator as an input adaptive feature. The instability oscillations are shown to occur in those situations in which one might predict small signals to be produced by an initial error sensing element in the system. It is suggested that one type of adaptive function is to vary the gain of the controller or error correcting portion of the system and hence the total open loop gain. When situations then arise that markedly increase open loop gain, instability oscillations result.

Finally, the system is shown to behave as if it were not a sampled data system, but rather operates on data flow continuously. □

REFERENCES

1. Campbell, F. W. and Robson, J. G.: High Speed Infrared Optometer. J. Opt. Soc. Amer., 49:268, 1959.

2. Stark, L., Takahashi, Y., and Zames, G.: Non-

linear Servo-analysis of Human Lens Accommodation. IEEE Trans. Systems Sci. Cybernetics., SSC-1:75, 1966.
3. Stark, L. and Sandberg, A.: A Simple Instrument for Measuring Eye Movements. MIT Quart. Prog. Rep., 62:268, 1961.
4. Campbell, F. W. and Westheimer, G.: Dynamics of Accommodation Responses of the Human Eye. J. Physiol., 151:285, 1960.
5. Campbell, F. W., Robson, J. G. and Westheimer, G.: Fluctuations of Accommodation Under Steady Viewing Conditions. J. Physiol., 145:579, 1959.
6. Young, L. R. and Stark, L.: A Discrete Model for Eye Tracking Movements. IEEE Trans. on Military Electronics, MIL-7:113, 1963.
7. Young, L. R. and Stark, L.: Variable Feedback Experiments Testing a Sampled Data Model for Eye Tracking Movements. IEEE Trans. of Prof. Tech. Group on Hum. Factors in Electronics. HFE-4:38, 1963.
8. Robinson, D. A.: The Mechanics of Human Smooth Pursuit Eye Movement. J. Physiol., 180:569, 1965.
9. Troelstra, A., Zuber, B. L., Miller, D., and Stark, L.: Accommodative Tracking: A Trial and Error Function. Vision Res., 4:585, 1964.
10. Campbell, F. W., Westheimer, G. and Robson, J. G.: Significance of Fluctuations of Accommodation. J. Opt. Soc. Amer., 48:669, 1958.
11. Stark, L., Iida, L., and Willis, P.: Dynamic Characteristics of the Motor Coordination System in Man. Biophys., 1:279, 1961.
12. Stark, L., Vossius, G. and Young, L. R.: Predictive Control of Eye Tracking Movements. IRE Trans. Hum. Factors Electronics, HFE-3:52, 1962.
13. Alpern, M.: Variability of Accommodation During Steady Fixation at Various Levels of Illuminance. J. Opt. Soc. Amer., 48:193, 1957.
14. Fincham, E. F., and Walton, J.: The Reciprocal Action of Accommodation and Convergence. J. Physiol., 137:488, 1957.
15. Alpern, M. and Ellen, P.: A Quantitative Analysis of the Horizontal Movements of the Eye in the Experiment of Johannes Muller—I Method and Results. Amer. J. Ophthal. 42:289, 1956.
16. Morgan, M. W., Jr.: The Clinical Aspects of Accommodation and Convergence. Amer. J. Ophthal., 21:3011, 313, 1944.
17. Ogle, Kn. N. and Marten, T. G.: On the Accommodative Convergence and Proximal Convergence. Arch. Ophthal., 57:702, 1957.
18. Fincham, E. F.: The Accommodation Reflex and Its Stimulus. Communications, Brit. J. Ophthal., 35:381, 1951.

□

DYNAMICS OF THE SACCADIC EYE-MOVEMENT MECHANISM

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LAWRENCE STARK, M.D.[2]

INTRODUCTION

An investigation into the dynamic behavior of the human eye-positioning mechanism has yielded a mathematical model for this system. Various investigators have studied eye movements and obtained evidence that there are only three basic kinds of movements made by the eye in attempting to follow unpredictable target movements.[1,2] These movements are saccades (step-like movements), pursuit (ramp-like) movements or combinations of the two. The words "step-like" and "ramp-like" are used because the movements resemble steps and ramps but on an expanded time scale are seen to have a dynamic behavior throughout the saccades and at the beginning of the pursuit movements. Young developed a sampled-data model which predicts the amplitude and time of occurrence of these movements; however, because the dynamic effects are of a much shorter duration than the sampling period, 0.2 seconds, he was not concerned with these effects or the physical eye-movement mechanism through which they are introduced.[2]

Robinson[3] advanced the most realistic representation of the movement mechanism, making use of data gained through experiments with external loading on the eyeball as well as through experiments under normal operating conditions. However, the velocity curves of his model do not agree with the experimental data under normal operating conditions. Also, he fails to point out what portion of the driving force is attributed to the agonistic (shortening) muscle's increase in activity and what portion is attributed to the antagonistic (lengthening) muscle's decrease in activity. It will be seen that this is an important point.

Hyde,[4] Lion and Brockhurst,[5] and Dodge and Cline[6] all performed experiments with saccadic or step-like movements and reported data on average and peak velocities for different size movements. However, none of these proposed any theory or model. Westheimer[7] performed similar experiments, and while recognizing that there were nonlinearities present, suggested a linear, second-order model based on input-output properties of the overall system. His model parameters have no real physical significance.

For the investigation here a basic configuration of a controller driving a dynamic plant was assumed. Such a division seems quite natural with the human

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brain being taken as the controller, the nerve signals being the control variables and the eyeball, extraocular muscles, and orbit composing the plant.

The overall behavior of this system was investigated through eye-tracking experiments in which the target moved in a horizontal plane and the subject moved his eyes in an effort to follow the target. The plant itself was investigated through a literature search which was directed toward identifying and mathematically describing the various components of the plant through physiological and anatomical considerations. The shape of the control signals was estimated from electromyograms. The plant was then simulated on a computer and driven with control signals of the form estimated from the electromyograms. By comparing the movement behavior obtained from the simulation with the actual movement behavior as measured experimentally, the validity of the model was confirmed. Comparisons were made not only of displacement, but also of velocity thus providing a more severe test than displacement comparisons alone.

It was found that the plant is quite slow and highly overdamped with most of the damping residing in the extraocular muscles and that this damping is proportional to the control signals of the respective muscles.

The damping of a shortening and lengthening muscle were found to be quite different. For this reason a complete description of control behavior requires that one know not only the difference in the control signals for the agonistic and antagonistic muscles, but that one know each of these signals.

With the plant being so slow the system is able to achieve movements as quickly as it does only through driving the plant with an extra burst of agonist control signal and almost inhibiting the antagonist during the movement. It was found that if the controller operated with a minimum time policy, the eye movements could be achieved in one-fourth to one-half the time they actually require.

METHODS

In studying the overall behavior of the system, a moving target was presented to the subject and his resulting eye behavior recorded. The subject was sitting with his head in a fixed position. Five feet in front of him was a projection screen on which was focused a spot of light. This light beam originated in a stationary projector and was reflected off a vertical axis mirror galvanometer onto the screen. An on-line computer with a digital-to-analog converter was used to control the angle of the mirror galvanometer and thus move the target in a horizontal plane. The method used for detecting the subject's eye movements depends upon the differential amounts of light reflected from the iris and the sclera on both sides of the eye. With the subject looking straight ahead two photo devices, which formed part of a bridge circuit, were aimed at the border of the sclera and the iris of one eye. A small infra-red light was also focused on this eye. By careful adjustment of the photodevices and the small light, a linear relation between actual eye position and recorded eye position was obtained over a range of twenty-five degrees or more. A more detailed description of this method is given in Stark, et al.[1] Velocity was obtained by differentiating the position signal electrically, that is with an R-C-Operational Amplifier circuit.

The target signals consisted of quasi-random steps. The initial and final values of the steps were varied according to a 10×10 Latin square programmed into the computer prior to the experiment.

In addition to supplying the target signal, the computer was used in processing the subject's responses by means of an analog-to-digital converter.[8,9] The overall bandwidth from eye detection equipment to digital computer was 200 cps. A few experiments were run with 700

cps bandpass equipment and yielded no significant changes in indicated eye-movement behavior. For this reason and because the lower-frequency equipment had the advantage of built-in bias and gain control as well as instantaneous monitoring, most of the experiments were run with the lower frequency equipment.

The behavior of the eyeball in attempting to follow a step change in target position consists of a delay of 150 to 250 milliseconds and then a relatively fast movement called a saccade. The delay time which varies from time to time for a given subject was not of interest to us, for we were primarily concerned with the dynamic behavior. However, when averaging techniques were used to reduce stationary noise, the variable delay time created a problem. That is to say it would not make sense to average a saccade beginning at t = 150 msec with a saccade beginning at t = 250 msec to find the average dynamic behavior (t = 0 is defined as the time of the step in target position). For this reason, before averaging it was desired to shift the responses in time so that the saccades would all begin at the same time. This was achieved by first having the computer write the responses with appropriate titles on digital tape while the experiment was in progress. After the experiment was completed, a program was used which would read a response off tape, display the response on an oscilloscope and at the same time write the response into an array in the computer. By manually adjusting an input voltage to the analog-to-digital converter, the waveform displayed on the oscilloscope could be made to move along the time scale. Simultaneously the array within the computer was shifted an identical amount. When the response was suitably positioned, a switch was toggled which caused the waveform with its new time origin (i.e., the shifted array) to be read into the averaging part of the program. The criterion used in positioning responses from the same type stimulus was to synchronize their velocity peaks. The averaged waveform was obtained via punched cards or a plot.

PLANT MODEL

The model for the dynamic plant is shown in Fig. 1a. The derivation of this model is given in References 8 and 10. Space does not permit this derivation to be presented in detail here; however, some comments should be made concerning the relation of model parameters to the physical system.

In Fig. 1a J represents the moment of inertia of the eyeball about its vertical axis. Assuming a rigid sphere of unit density, with radius 11 millimeters, we computer J to be 2.7 dyne cm sec^2/rad. In terms of tension referred to the muscles, this is 4.3×10^{-5} grams tension/(deg/sec^2). We know that the eyeball is not rigid, and that a more accurate model might be a series of spherical shells connected successively by springs and dashpots. However, for simplicity and also because the effect of the inertia was expected to play a very small role in the overall behavior, the cruder rigid-sphere model was retained. It was found later through simulations that increasing the calculated moment of inertia by a factor of ten had almost no effect on the output behavior indicating that one could even ignore this moment of inertia completely.

Of the six extraocular muscles used in controlling the eyeball, the lateral and medial recti are primarily responsible for executing horizontal movements. Since this investigation was restricted to such movements, only these two muscles were considered in deriving the model.

Referring again to Fig. 1a K_p represents the net passive elastance of the lateral and medial recti. This spring has its equilibrium position at zero degrees, i.e., with the eyeball pointed straight ahead. The K_a's represent the elastance in series with the active portion of the muscles. This active portion of the mus-

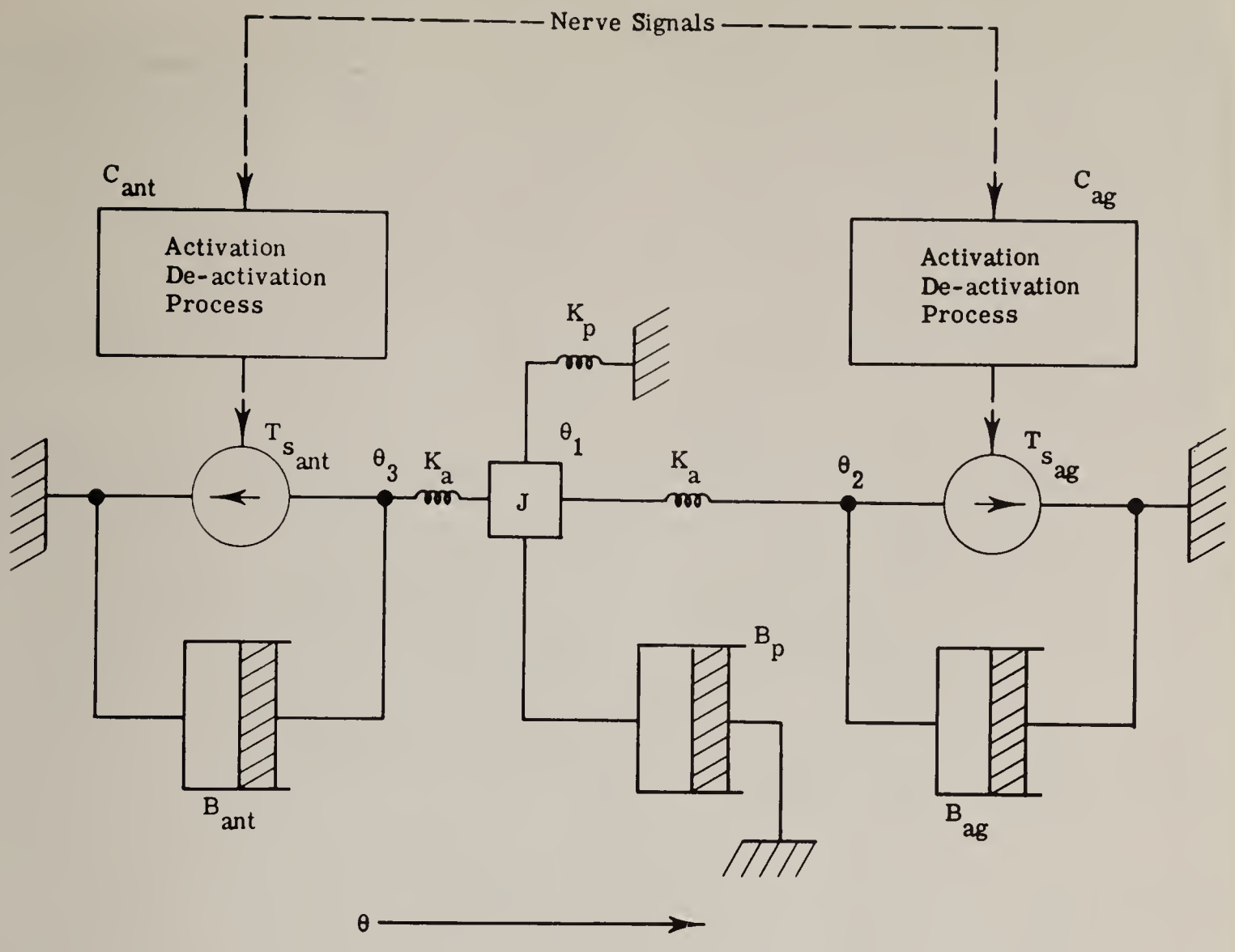


Fig. 1a.—Model for dynamic plant with parameters: $K_a = 1.8$ gm/deg; $K_p = 1.5$ gm/deg; $B_p = .018$gm sec/deg; $\tau_{ACT} = 4$ msec; $\tau_{DE\text{-}ACT} = 8$ msec; $T_s\,(0°) = 37.5$ gm; $B_{ag} = 1.25\ T_{s_{ag}}/(900 + \theta)$; $B_L = 3\ T_{s_{ant}}/900$; $T_{sMAX} = 200$ grams.

cle, often referred to as the contractile element, has been modeled as a tension source, T_s, in parallel with a nonlinear damping B. The K_a's and K_p are obtained from plots of stretch versus tension and estimated to be: $K_p = 1.5$ gm/deg and $K_a = 1.8$ gm/deg.

To obtain B, use was made of the work of Hill[11] in which he developed an equation relating force to velocity for various degrees of excitation (T_s). Using Hill's formula, B for a shortening muscle was found to be:

$$B_{ag} = 1.25\ T_{s_{ag}}/(900 + \theta) \qquad (1)$$

where θ represents the velocity of shortening of the contractile element and $T_{s_{ag}}$ represents the tension source of the shortening muscle.

Katz[12] showed that a lengthening muscle behaves quite differently than a shortening muscle. Making use of his work B for a lengthening muscle was found to be:

$$B_{ant} = 3\ T_{s_{ant}}/1500 \qquad (2)$$

where $T_{s_{ant}}$ represents the tension of the tension source of the lengthening muscle.

The parameter B_p of Fig. 1a represents the damping between the eyeball and the socket. Making use of an experiment by Robinson in which the eye of a subject attempting to look straight ahead was forcibly turned to an angle of 12 degrees and then released, B_p was estimated to be .018 gram sec/deg.

Since B_{ag} and B_{ant} are different and are each functions of the tension sources, it is seen that the behavior of the eyeball will depend not only on the difference between the tensions of the tension sources, but on each of the tension sources

as well. This fact makes it important to know if there is a steady-state level of tension in these sources even when the eye is looking straight ahead.

Making use of the work of Breinin[13] in electromyography showing integrated muscle potential versus steady-state eye position, the steady-state tension in the tension sources of each muscle with the eye looking straight ahead was estimated to be 37.5 grams.

The final components of the model are the activation de-activation processes. These represent transient processes of which the inputs are the nerve signals called C and of which the outputs are the tension sources. Wilkie[14] describes an experiment designed to illustrate this process. The muscle used was a frog's sartorius at a temperature of 0°C. Wilkie's findings were that the time constant for de-activation was approximately 100 milliseconds and the time constant for activation many times shorter. It is difficult to know how to adapt these results to our situation. No doubt the extraocular muscles operating at body temperature are much faster than this. For lack of a better estimation, we shall take the time constant for de-activation of the extraocular muscles as ten milliseconds and that for activation as less than one millisecond.

The forms of the control signals, C_{ag} and C_{ant}, during a saccadic movement are estimated from electromyograms by Jampolsky et al.[15] to be piecewise constant as shown in Fig. 1b. The next step is to simulate the model, drive it with signals of the form shown in Fig. 1b and compare the resulting behavior with the actual eye movement behavior as measured experimentally.

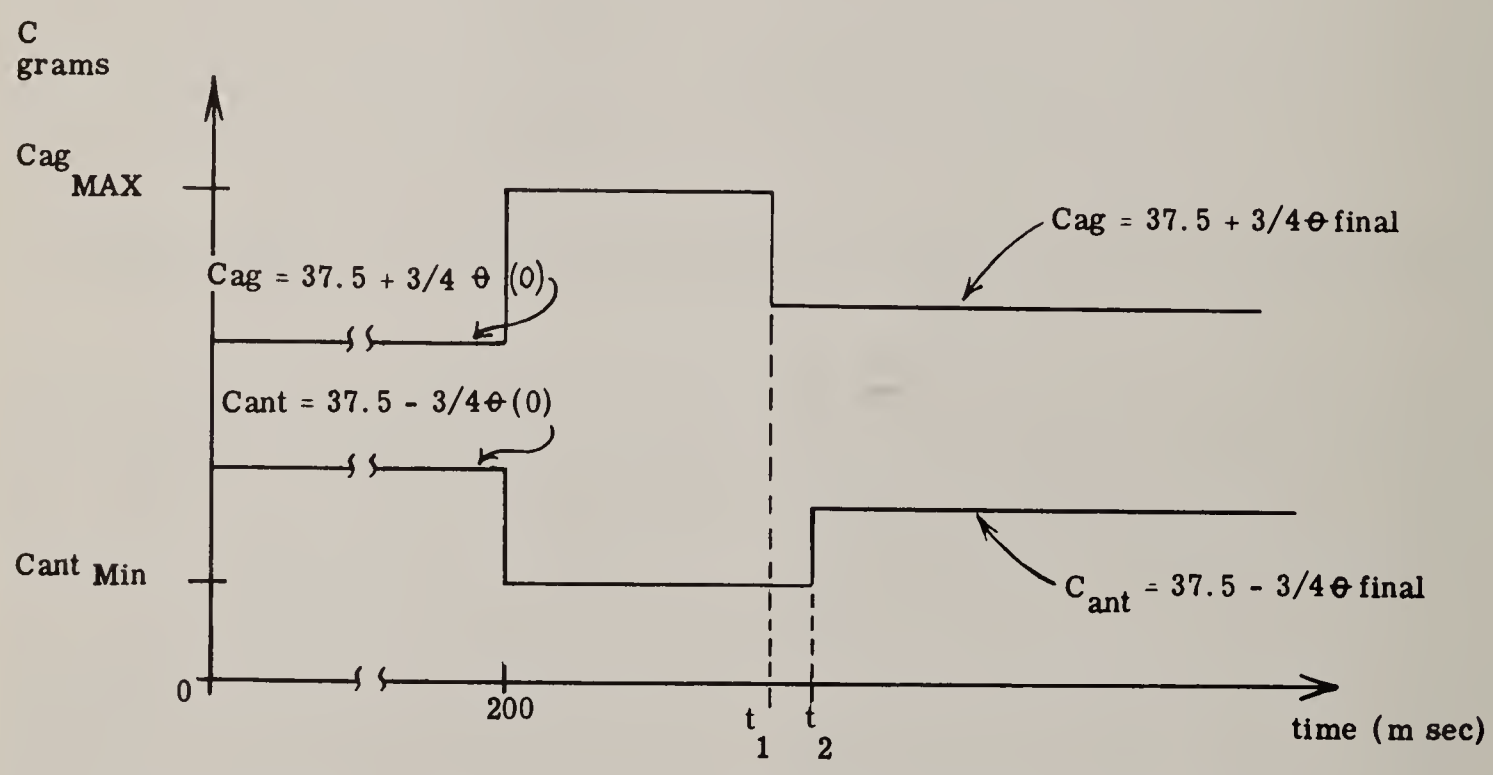


Fig. 1b.—Estimated control signals during a saccadic movement originating at zero degrees.

RESULTS

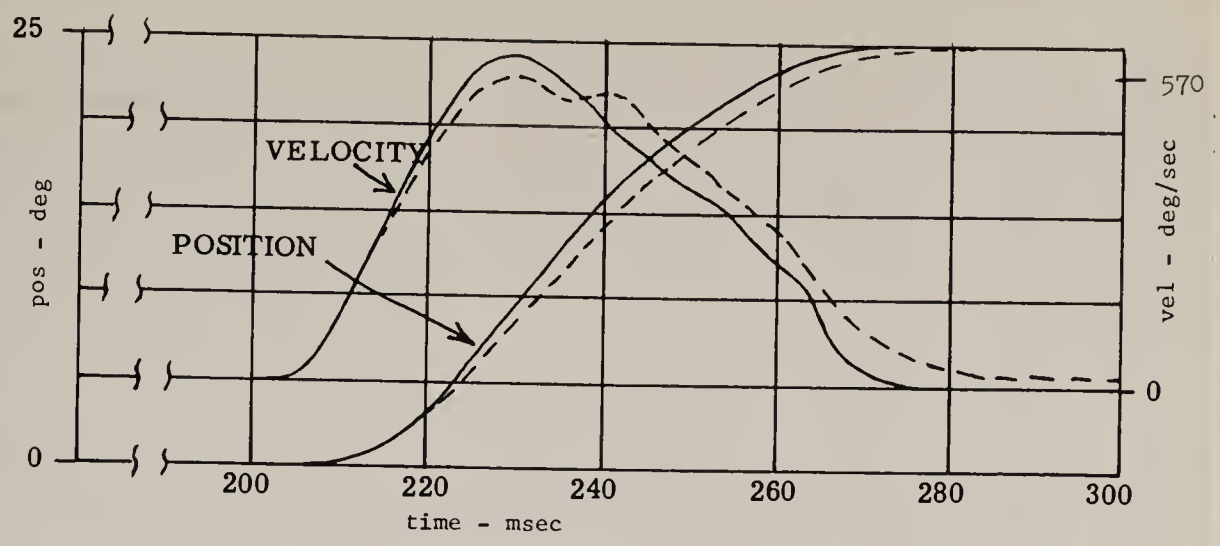
Fig. 2 gives position and velocity curves for various saccadic movements along with data describing the control signals. For comparison the experimental and simulated results have been superimposed. The experimental curves represent averages of ten or more samples. The similarity of the position curves is obvious. The velocity curves show slightly more deviation but are still quite similar. Of course ideally it would be desirable to also compare acceleration and higher derivatives. However, such comparisons would require equipment of extremely

$C_{ag_{MAX}} = 75$

$C_{ant_{MIN}} = 2$

$t_1 = 250$

$t_2 = 260$

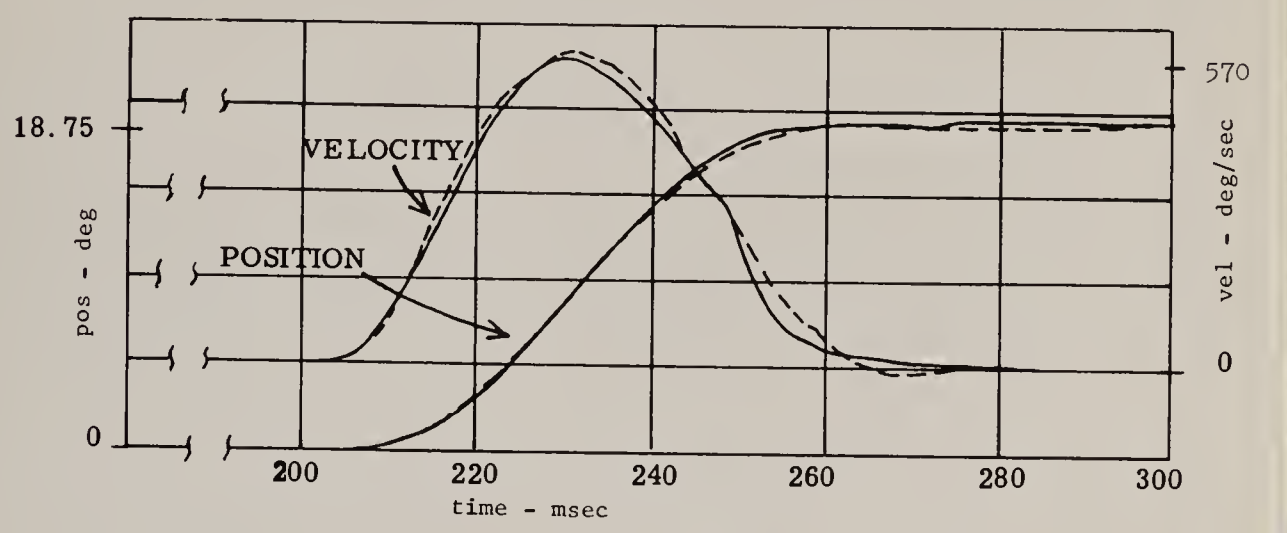


$C_{ag_{MAX}} = 65$

$C_{ant_{MIN}} = 2$

$t_1 = 238$

$t_2 = 245$

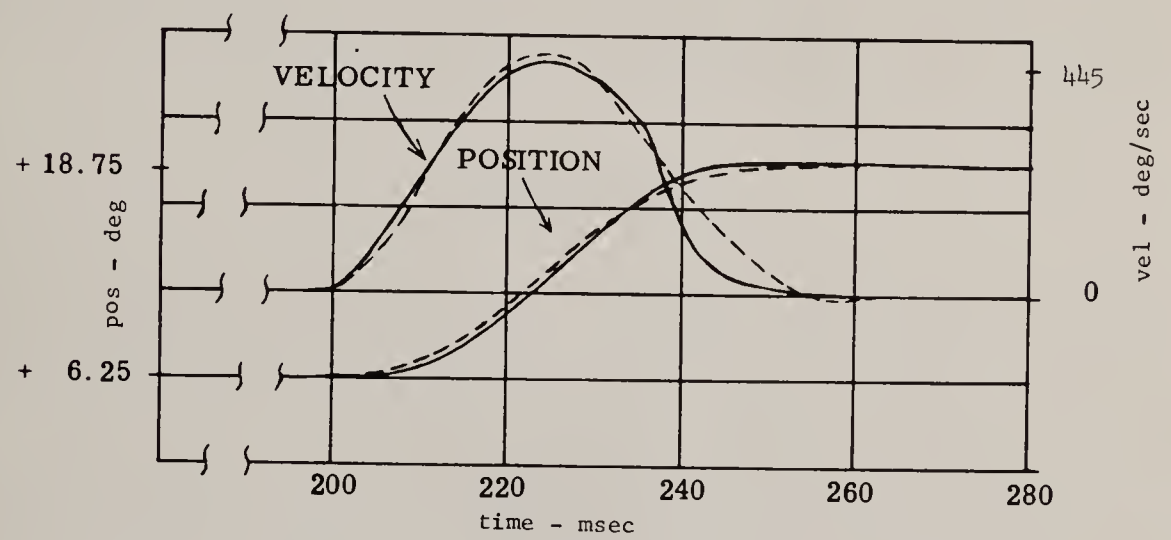


$C_{ag_{MAX}} = 65$

$C_{ant_{MIN}} = 3$

$t_1 = 231$

$t_2 = 237$

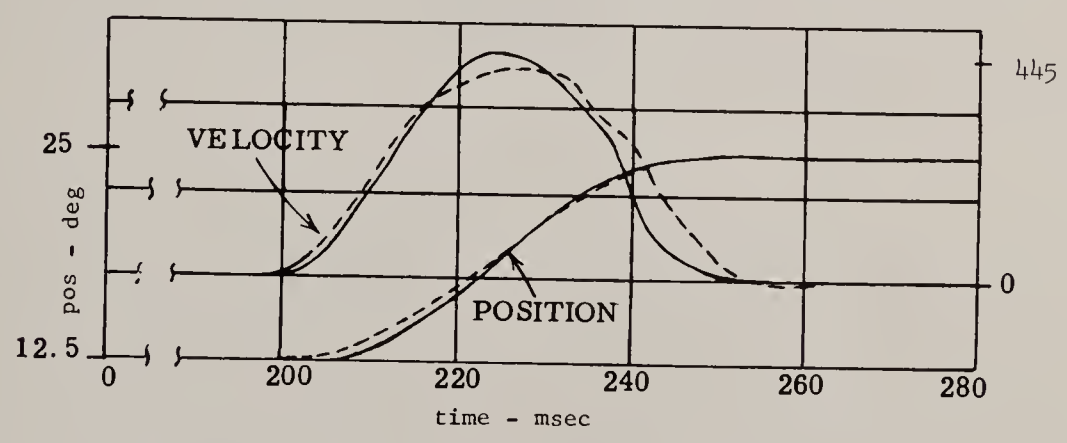


$C_{ag_{MAX}} = 70$

$C_{ant_{MIN}} = 3$

$t_1 = 231$

$t_2 = 237$



$C_{ag_{MAX}} = 75$

$C_{ant_{MIN}} = 3$

$t_1 = 221$

$t_2 = 227$

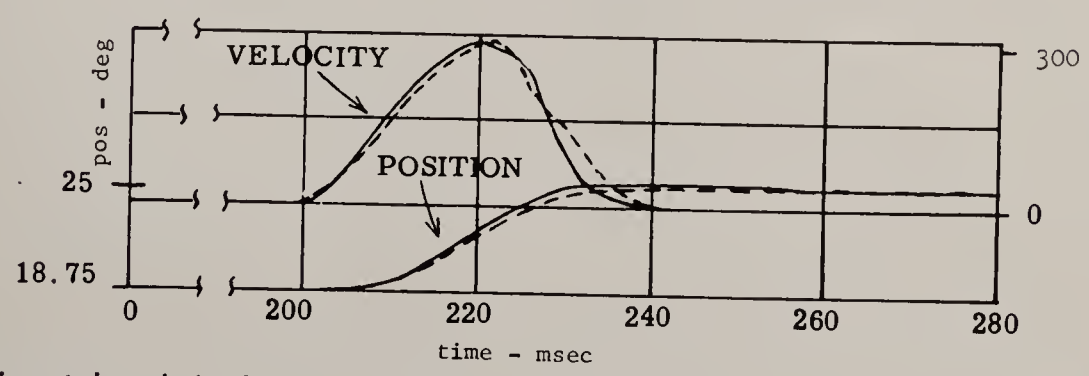


Fig. 2.—Experimental and simulated saccadic movement. Experimental curves are dashed; simulated are solid. (——— experimental, ——— simulated)

high bandwidth for accuracy and the measurements would no doubt contain much noise.

The model parameters were adjusted to give best agreement between theoretical and experimental results. Final values are given in Fig. 1a.

As a point of interest it was decided to investigate the minimum time behavior of the system, i.e., how would the system behave if the policy of the controller were to minimize the time required to execute a movement? The maximum tension available from the tension sources was estimated to be 200 grams. With this constraint, the minimum time behavior was determined and simulated. The results revealed that the actual movements require two to four times as long for completion as would be necessary if the system operated with a minimum time policy.

CONCLUSIONS

A model for the human eye-movement mechanism has been developed. By assuming as inputs control signals of the form suggested by electromyography the resulting model output behavior was found to be quite similar to that of the actual system as measured experimentally, lending support to the validity of the model. It was found that the plant itself is quite slow with most of the damping being in the muscles and this damping being proportional to the level of muscle activation. The moment of inertia of the eyeball was found to be insignificant. The theoretical minimum time behavior indicated that actual movements require from two to four times as long for execution as would be the case if the controller operated with a minimum time policy.

SUMMARY

An on-line computer was used to experimentally measure the dynamic performance of horizontal eye movement saccades. A mathematical model based upon physiological measurements in the literature was assembled for the plant—eyeball and eye muscles, and the controller signals—EMG. Simulation of the model with parameter adjustment led to reasonably close agreement between model and experimental overall behavior. It was found that actual movements require about three times as long for completion as would be necessary if the system operated with a minimum time policy. □

REFERENCES

1. Stark, L., Vassius, G., and Young, L. R.: Predictive Control of Eye Tracking Novements. IRE Trans. Hum. Factors Electronics. HFE-3:52-57, 1962.
2. Young, L. R.: A Sampled Data Model for Eye Tracking Movements. Sc.D. Thesis, MIT, 1962.
3. Robinson, D. A.: The Mechanics of Human Saccadic Eye Movement. J. Physiol., 174:245-264, 1964.
4. Hyde, J. E.: Some Characteristics of Voluntary Human Ocular Movements by Means of an Electrical Method. Arch. Ophthal., 48:1, 1959.
5. Lion, K. S. and Brockhurst, R. J.: Analysis of Ocular Movements by Means of an Electrical Method. Arch. Ophthal., 46:311-314, 1951.
6. Dodge, R. and Cline, T. S.: The Angle Velocity of Eye Movements. Psychol. Rev., 8:145-157, 1901.
7. Westheimer, F.: Eye Movement Responses to a Horizontally Moving Visual Stimulus. Arch. Ophthal., 52:932, 1954.
8. Cook, G.: Control Systems Study of the Saccadic Eye-movement Mechanism. Sc.D. Thesis, MIT, 1965.
9. Cook, G., Stark, L. and Zuber, B. L.: Horizontal Eye Movements Studied with the On-Line Computer. Arch. Ophthal., 76:589-595, 1966.
10. Cook, G. and Stark, L.: Derivation of a Model for the Human Eye-positioning Mechanism. Bull. Math Biophys., 29:153-175, 1967.
11. Hill, A. V.: Energy Liberation and "Viscosity" in Muscle. J. Physiol., 93:4, 1938.
12. Katz, B.: Anti-curare Action. J. Physiol., 95:286-304, 1939.

13. Breinin, G. M.: (Toronto, Ontario: The University of Toronto Press), p. 122, 1962.
14. Wilkie, D. R.: Facts and Theories About Muscle. 4:294-314, 1954.
15. Tamler, E., Marg, E., Jampolsky, A., and Nawratzki, I.: Electromyography of Human Saccadic Eye Movements. Arch. Ophthal., 62:657-661, 1959.
16. Cook, G. and Stark, L.: Dynamics of the Saccadic Eye-Movement Mechanism. Proc. Symposium Biomed. Engin., 1:356-359, 1966.
17. Stark, L.: Neurological Feedback Control Systems. Advances Bioeng. Instrumentation, 4:289-385, 1966. □

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SAMPLING OR INTERMITTENCY IN THE HAND CONTROL SYSTEM

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LAWRENCE STARK, M.D.[2]

INTRODUCTION

We have examined the control system for human hand movement, using the approaches of several different disciplines. In studying the performance of the system, its limits, and possibilities from the viewpoint of a human engineer, we have used a tracking situation and complex inputs to obtain a variety of frequency responses. We have utilized known facts and data from the physiological literature, and have also simulated muscle and muscle spindle dynamics to define the blocks within the total motor control system of man.[13] As neurologists, we have organized the "topology" of these physiological elemental blocks into a model in a manner that seems compatible with actual neurological organization as far as this is known. To further refine and assess our model, we have utilized studies in persons with neurological defects such as Parkinson's disease, and have studied the effects of drugs producing temporary paralysis of gamma efferent fibers. Finally, as control engineers interested in neurological control systems, we have used special experimental techniques such as opening loops by clamping methods in order to expose certain essential characteristics of this feedback control system.

Some of the characteristic features of our model, which we present and describe, have been derived from physiological information, some from our experimental results, and some remain untested assumptions. Ward,[20] Bekey,[1] Lemay and Westcott[8] have postulated sampled data models for the hand; Smith and Cortes[2] a "bang-bang" system; psychologists since Telford[18] have been interested in psychological refractory period and intermittency in voluntary responses; Russell, Tustin[19] and Elkind[4] have defined frequency characteristics of manual control; and work has been done in our group, the Neurology Section at Massachusetts Institute of Technology, (now at University of Illinois, Chicago Circle) defining physiological elements and neurological organization, studying experimentally and by simulation transient and steady state behavior[14] and sampled data characteristics of hand and eye tracking systems.[11]

After description of the equipment, the

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experimental section describes results from four types of inputs: closed loop transients, open loop and variable feedback transients, closed loop predictable signals.

In the discussion section we evaluate our model and relate our work to previously published research in this field as well as to other models. The evidence for intermittency in the hand control system is developed in full during an expanded discussion of the various experiments, observations and assumptions of our studies.

In the conclusion we attempt to summarize the present status of our knowledge of the human control system for hand movement.

THE MODEL

Sampled Data Characteristics

Recent studies have suggested that the eye movement tracking system can be treated as a sampled data system[21,22] since the discrete nature of sampled data systems is in some sense similar to the notion of a refractory period, a common phenomenon in neurophysiology. Other discontinuous control systems such as quantized systems have properties in common with sampled data systems, and indeed the hand movement system demonstrates characteristics of quantization as well.[15]

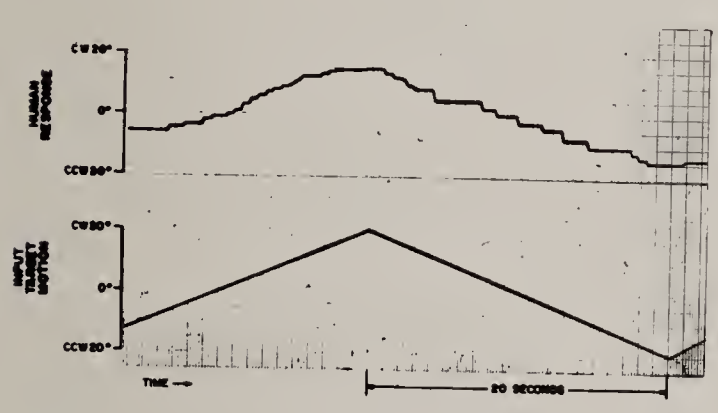


Fig. 1.—Discontinuous change of hand position to slow target ramps.

When slowly moving ramps are used as input target signals, and the subject is tracking this input with a device that offers very small mechanical impedance, a response similar to the one shown in Figure 1 is seen. The output response consists of step-like changes in position which occur with irregular intervals and amplitudes. The output signal rotary motion transducer had an effectively infinite resolution, and neither friction nor any other component of the mechanical impedance of the transducer was of sufficient magnitude to play an important role in the dynamics of the system.

When pulses of varying width are used as input target signals and are presented irregularly in time, a response that is similar to that shown in Figure 2 (upper) is obtained. There are delays of approximately 150 to 250 msec before the rapid response motions occur for both leading and trailing edges of the input target motion. This delay in response has several components in addition to nerve conduction time and is sometimes called the "psychological refractory period."[18]

When a pulse of extremely narrow width is supplied unpredictably as an input target motion, a normal delay occurs before the response movement to the leading edge of the input motion as Figure 2 (middle) illustrates. However, the response movement to the trailing edge of the input motion has a much more prolonged delay, 400 msec, as in the case illustrated in Figure 2 (middle). This prolonged delay can be accounted for as a normal refractory period that starts after the initial response motion, rather than being triggered by the trailing edge of the input target. This behavior would be characteristic of a sampled data system.

For a motor coordination sampled data system with the transient responses shown in Figures 1 and 2, the frequency response to wide bandwidth inputs could demonstrate a peak at one-half the sampling frequency, or at approximately 2 to 3 cps, as well as an absence of coherent

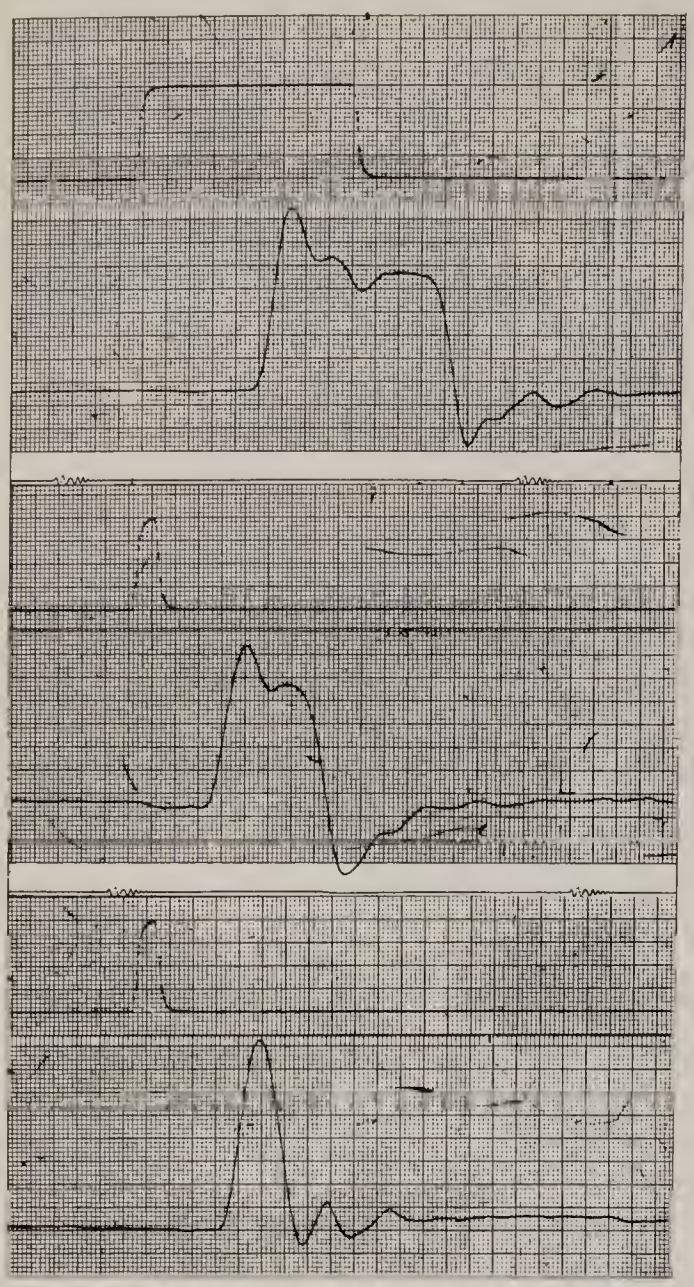


Fig. 2.—Responses to unpredictable wide pulse, unpredictable narrow pulse, and predictable narrow pulse showing respectively, delay, refractory period, and input-adapted preprogramming.

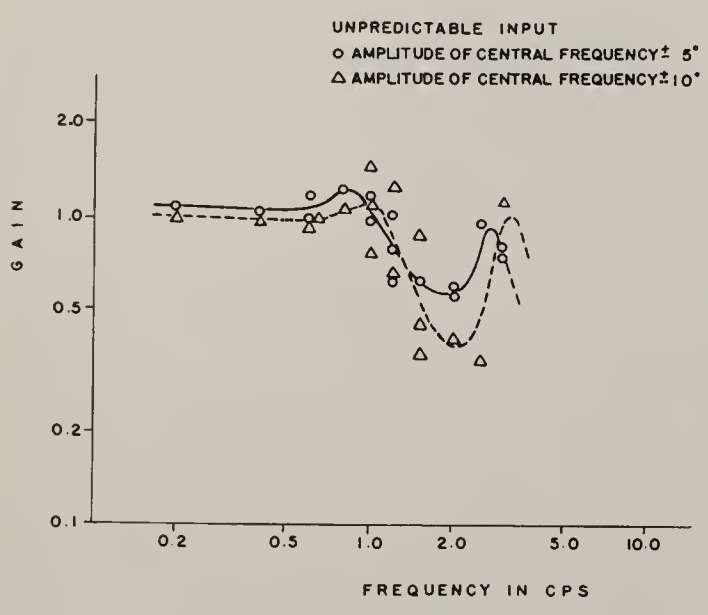


Fig. 3.—Effect of amplitude on frequency response gain data.

tracking characteristics at frequencies greater than this peaking frequency. There exists very little experimental data that clearly support the occurrence of this suggested peaking frequency since most of the experiments have used input bandwidths with either much lower frequencies than 3 cps or else too little power at these higher frequencies to obtain effective responses necessary to demonstrate the peak. Bekey,[1] in the most complete study of sampled data properties of the manual tracking control system, was able to show peaking at sampling frequencies only in spectral curves of error. However, Stark, Iida, and Willis[14] have described steady state frequency response experiments that were not limited by these undesirable input spectrum characteristics. This clearly defined peak in the response spectrum in Figure 3 supports the idea that the human motor coordination system can be treated as a sampled data control system.

The adequacy of representing the hand movement system as a feedback control system has been shown by various human engineering investigators.[4,7,9,10,19] Further, on the basis of our own experimental results such as short pulse (Figure 2) and the ramp responses shown in Figure 4, as well as the findings of others,[1,6,20] we decided that some kind of intermittency should be included.

For unpredictable inputs, the human tracking system acts as a position feedback control system with important discontinuous properties in the frequency range of interest. Its intermittency is related to an interesting alternation of control of the muscle by ballistic voluntary inputs and by a stabilizing proprioceptive reflex loop. The actuating signal of the system includes a combination of error and input (pursuit tracking) which compensates for some of the inherent delays. For predictable inputs, different continuous models which include ideal predictors are applicable. The model to be presented has a number of characteristic features, each of which will be discussed in detail, justified by experiment

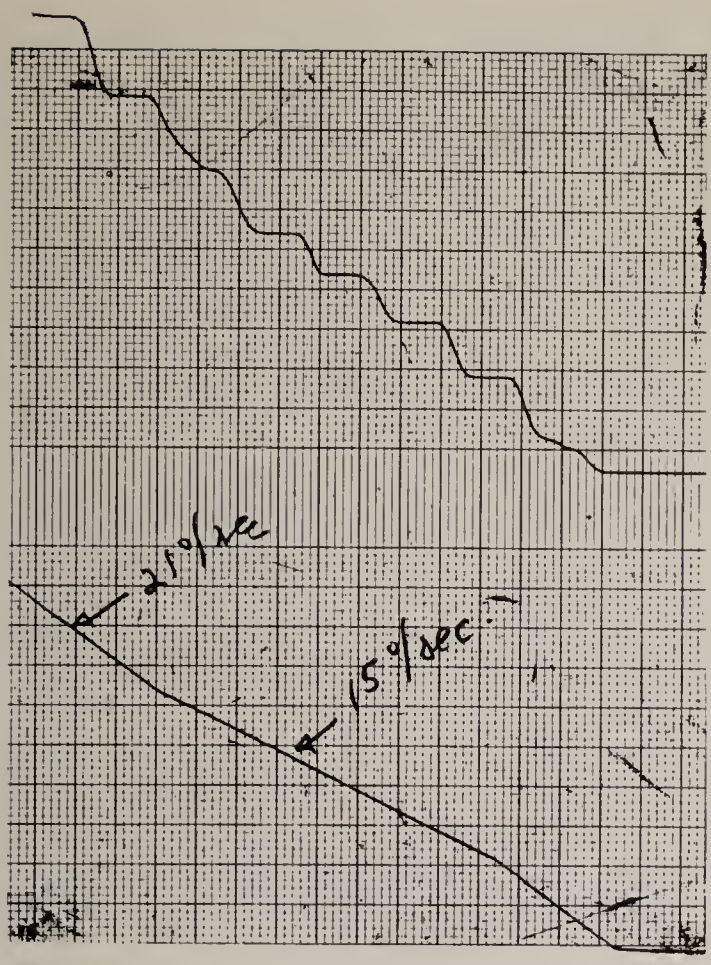


Fig. 4.—Intermittent response to unpredictable ramp inputs.

where possible, and related in the discussion, to results in the literature.

The Model

The model for pursuit tracking of unpredictable inputs is presented in Figure 5a in block diagrammatic form. Note: a) the visual feedback path and the integrator in the loop which makes the system a position servo; b) the additional proprioceptive feedback path; c) the switch providing an intermittency or quasi-sampled data action; d) the alternation between voluntary and reflex action for control; and e) that the observation of the input allows for some delay compensation through the lead term $(1 + k_2 s/k_1)$.

This block diagram necessarily includes elements from the visual, central nervous, and muscular systems.

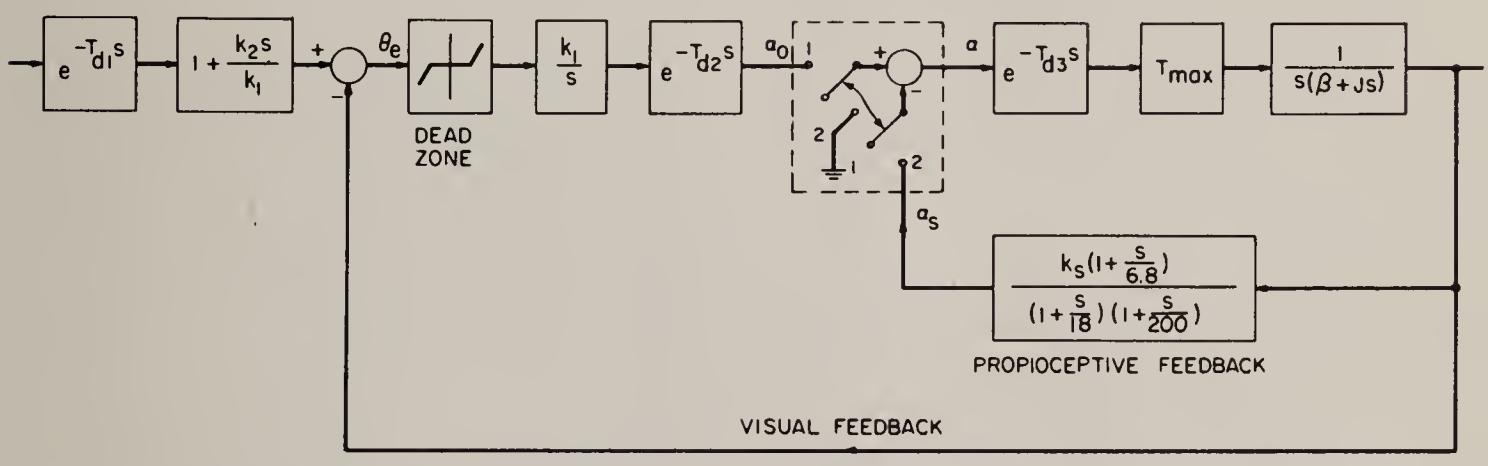


Fig. 5.—(a) Model for pursuit tracking of unpredictable inputs. (b) Open loop and variable feedback arrangement.

EXPERIMENTAL METHOD

The experimental arrangement, shown in Figure 6, includes the "light-coordination machine" and peripheral equipment for the analysis and generation of signals. Certain modifications were made in the apparatus in order to adapt it for rapid transient visual inputs, and to permit mechanical impulses to be injected.[13]

The light-coordination machine consists of a linear mirror galvanometer which transforms an electric signal into a display of a light pencil, a screen, a pointer, and an angular potentiometer as the mechanical-to-electrical transducer. The subject tried to follow and reproduce the display by rotation of his wrist. The response of the subject (rotation of the wrist) was measured by a precision continuous (infinite resolution) potentiometer, and, in addition to this

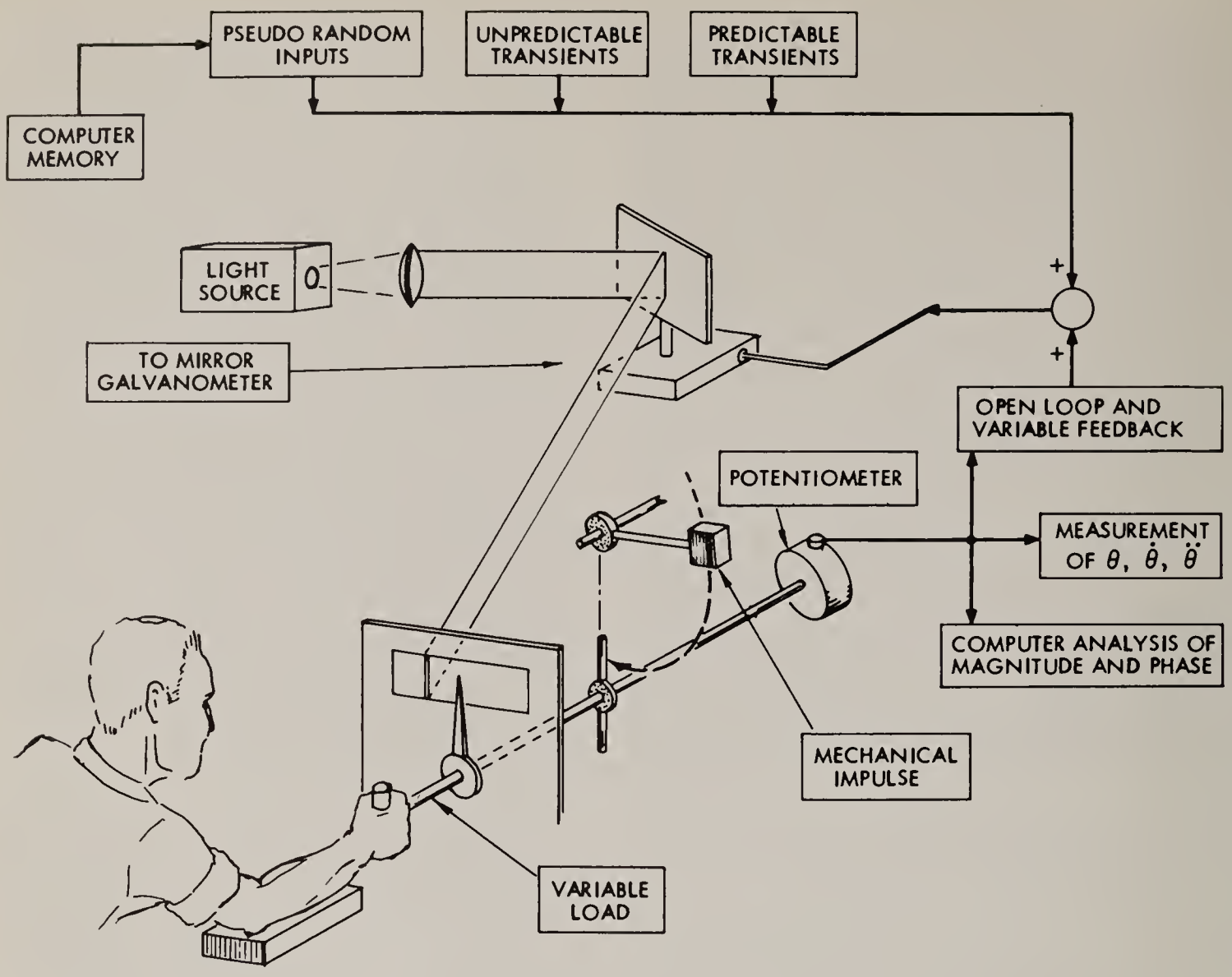


Fig. 6.—Sketch of apparatus.

angle e, we could obtain $\dot{e}$ and $\ddot{e}$ by differentiating.

The handle of the machine was very light and had negligible friction. When no extra load was added, it acted as a small inertia load on the arm. Accelerations as high as 400°/sec.^{2} were recorded, and the apparatus required very small forces; much less than 100g. This was a favorable feature since the apparent viscosity of the muscle increases with the degree of activation.

The method of studying the rotation of the wrist of an awake cooperative subject has been described in an earlier paper where impulses, pulses, and steps, all with unpredictable times of occurrence, were contrasted with successions of regular square waves of target position in addition to single sinusoids, and sums of incommensurate sinusoids, the pseudo-random signal previously described.[14]

Peripheral equipment of the experimental arrangement included function generators, filters, operational amplifiers set for signal transformation, recorders, measuring equipment, a pendulum for application of mechanical impulses, and a computer with digital-to-analog and analog-to-digital conversion equipment. The computer was used for the frequency domain characterization of the human operator using programs developed by our group in the Neurology Section of the Electronic Systems Laboratory at Massachusetts Institute of Technology. The computer produced a combination of sinusoids of arbitrary magnitude and phase, and it made Fourier analysis of the operator's response to these signals.

Eye-Hand Comparisons

Because of the large variation in response of both the hand and the eye systems with different subjects, with minor modifications of the experimental

apparatus, and with time, we decided to measure both of these systems responses simultaneously.

The eye muscles have considerable power with respect to their constant load, the eyeball, and show faster rise times than the hand especially when tracking rapidly alternating signals as shown in Figure 7c. Examples of eye and hand responses both recorded simultaneously to irregular steps and slower regular steps are also illustrated in Figure 7; for these inputs the eye has shorter response times than the hand.

At moderate frequencies (0.7 to 1.0 cps) the hand develops prediction faster and to a greater extent than the eye. At higher frequencies (1.2 cps) the hand shows considerable prediction, while the median eye response time starts to lag in spite of the higher frequency characteristics of the actual movement dynamics of the eye. At low frequencies, there is some correlation evident between eye and hand response times as is shown in Figure 7.

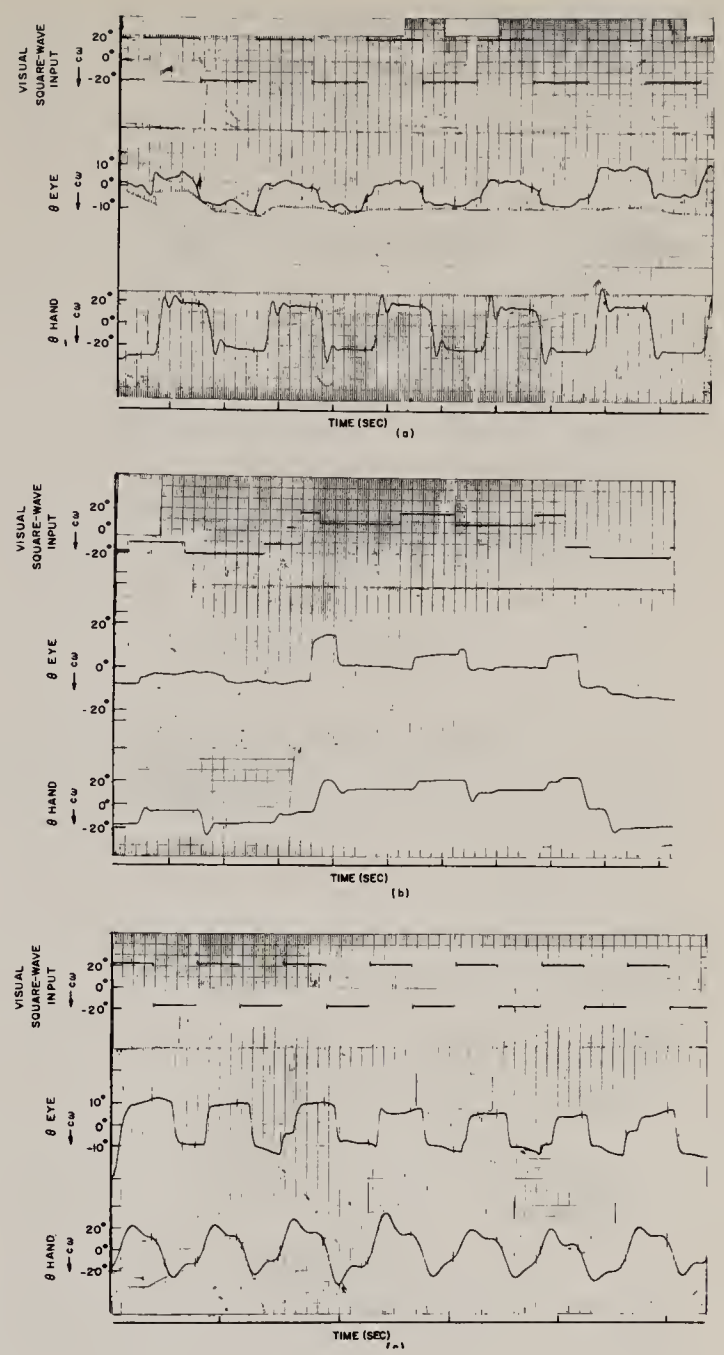


Fig. 7.—Eye and hand steps responses to random (b) and regular target square waves (a) 0.5 cps and (c) 2.5 cps.

EXPERIMENTAL RESULTS

Closed Loop Transients (Unpredictable Inputs)

Closed loop transients included visual pulses and approximations to impulses, mechanical impulses, visual steps and ramps. Examples of typical performances are presented.

a) *Input pulses:* Responses to input pulses are shown in Figure 8. For unpredictable short pulses there were intervals from 0.15 to 0.30 sec. between the two halves of the response, as can be seen from Figure 8c and 8d. This was no longer true for predictable short pulses shown in Figure 8e. Notice also the fairly consistent overshoots in the initial correction, the oscillatory hunting, and the decrease of velocity after the proper output level is achieved. The addition of moderate load seems to decrease natural frequency and the acceleration of the arm.

Figures 9 and 10 show the responses to visual and mechanical impulses (13). The visual impulse was a very narrow light pulse of more than 20°, and the mechanical impulse was a disturbance applied to the pointer axis by means of the pendulum. It is of interest to fit these "impulse responses" to a simple model, a second order system, which thus characterizes

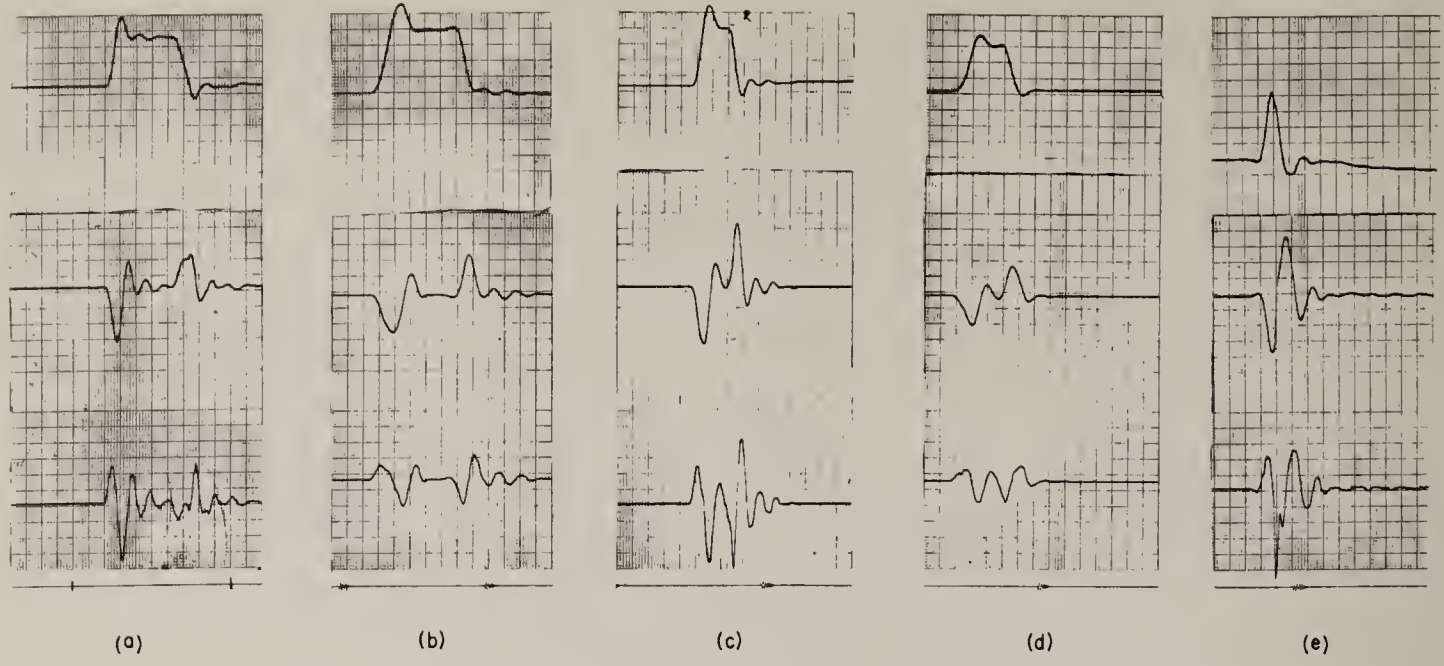


Fig. 8.—Responses to pulse inputs: (a) 400 msec pulse; (b) 400 msec pulse, inertia and friction added to handle; (c) 100 msec pulse; and (d) 100 msec pulse, inertia and friction added to handle; (e) predictable input, response to 100 msce know pulse. Abscissa scales show time in second.

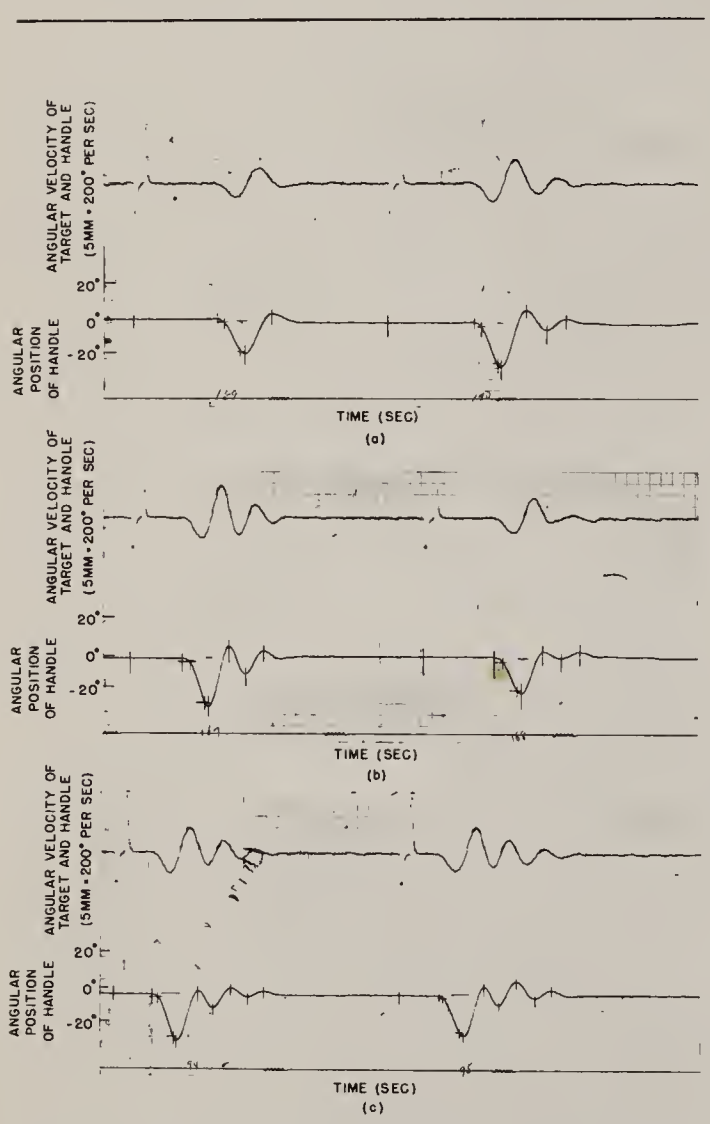


Fig. 9.—Visual impulse responses with velocity indicated: (a) relaxed condition; (b) moderately tense condition; and (c) very tense condition.

the motor end of the control system. The mechanical impulse response looks like a second order system; the natural frequency for the relaxed subject is 3 cps and the camping ratio is 0.15; for the

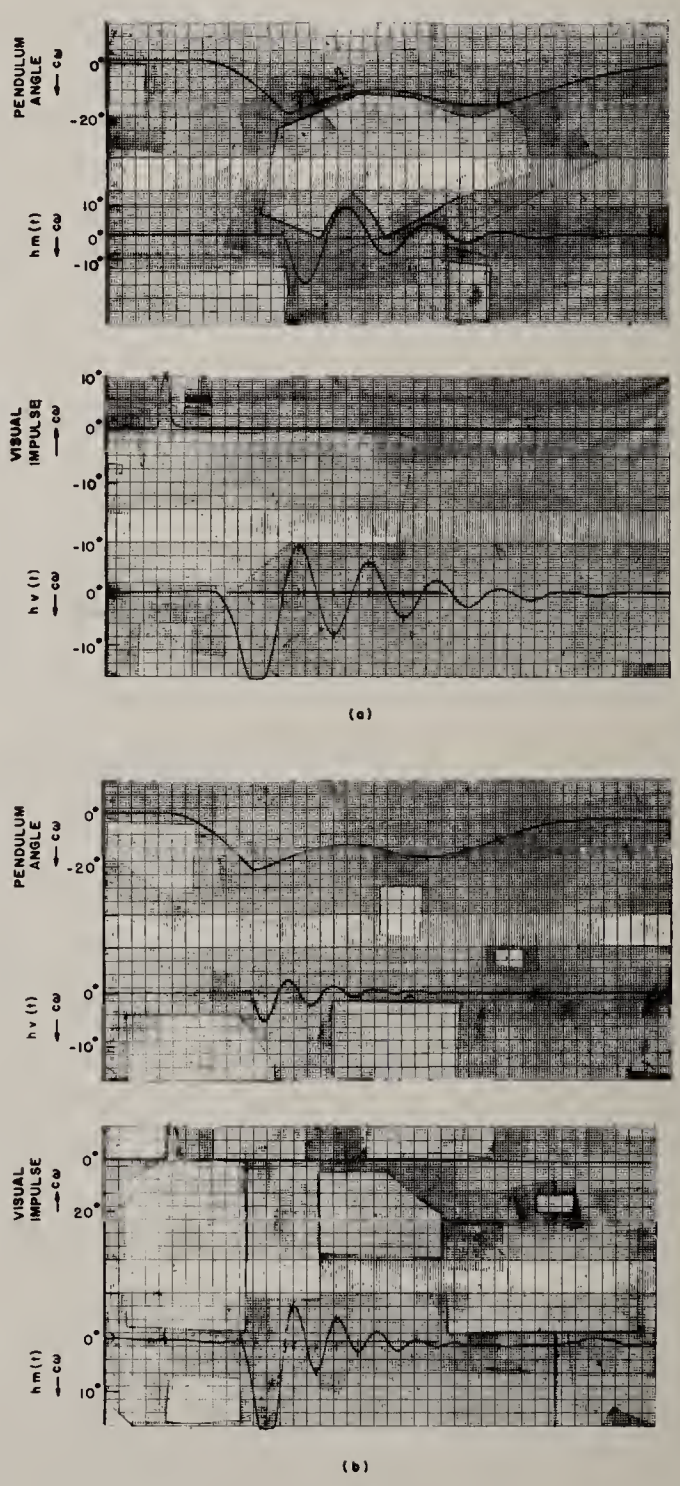


Fig. 10.—Impulse experiments.

tense subject the natural frequency is 5 cps and the damping ratio is 0.20. The visual impulse response is characterized by two high gain corrections, and a subsequent part representing an oscillatory decay. The first part of the response looks like an on-off action. After the first correction the situation can hardly be called unpredictable.

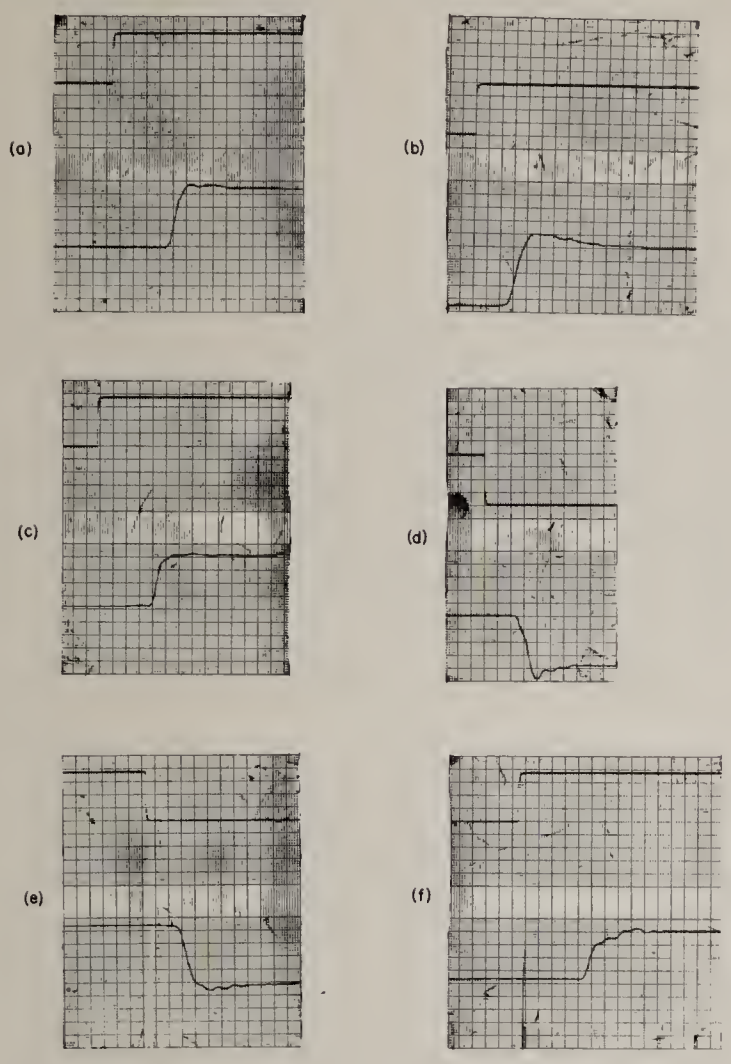


Fig. 11.—Six types of step response: (a) 11 cases out of 40; (b) 7 cases; (c) 7 cases; (d) 5 cases; (e) 5 cases; and (f) 3 cases. Size of steps 20 degrees. Time scale 100 msec/large division.

b) *Input steps:* The responses of the hand control system to unpredictable steps have most of the characteristics already noted for pulse responses, and a few others. Figure 11 shows the main types of responses, whose delay varies between 200 and 450 msec. Overshoot in the initial correction is usual, and is followed by oscillations (6.8 cps). The possibility of two-mode action is clearly seen in Figure 11b, c, e, and f. Figure 12 shows the output and its velocity and acceleration for unpredictable and predictable steps. The velocity graphs consist of a triangle followed by decaying oscillations, which for the predictable case (Fig. 12e) are of minor importance.

The acceleration consists of a pulse which carries the arm to the desired position followed by several alternating pulses during a breaking or clamping period. There is no overshoot for the predictable case, and the first acceleration pulse is followed by a deceleration pulse before reaching the desired position thus suggesting a different action; small acceleration oscillations follow.

Studies of reaction time distribution for step responses have been done by

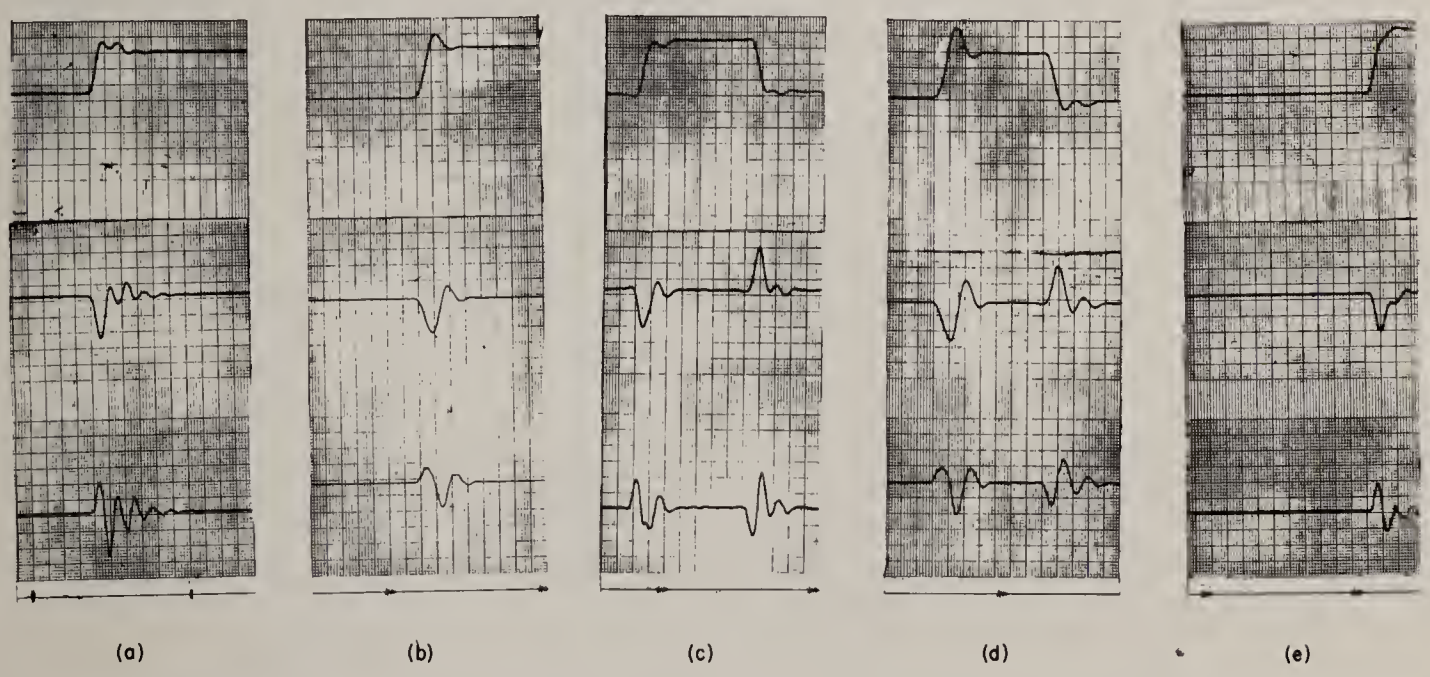


Fig. 12.—Step responses: (a) and (b) unpredictable; (c) and (d) unpredictable with inertia and friction added to handle; and (e) predictable—response to known step after training. Upper trail is position; middle trail is minus velocity; and lower trail is acceleration.

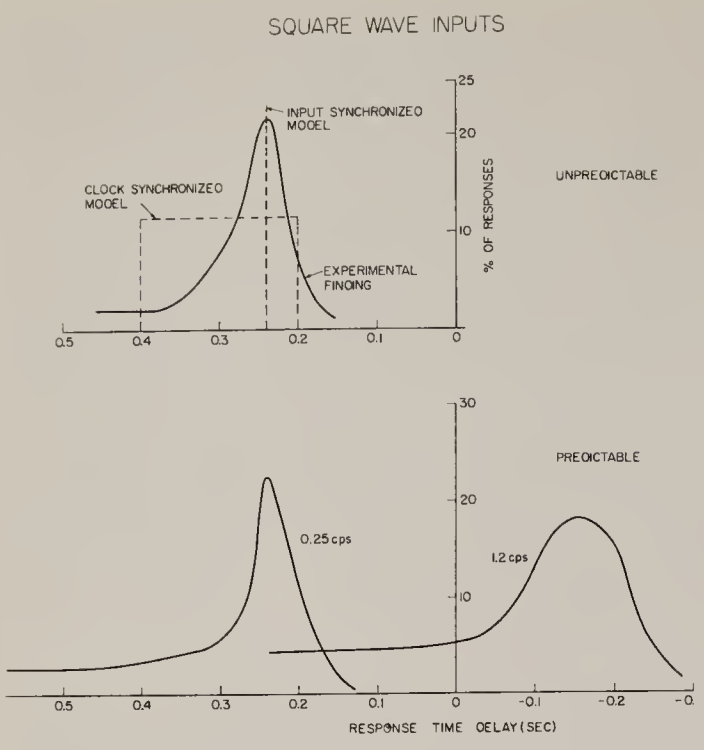


Fig. 13.—Reaction time distributions for responses to both unpredictable steps and predictable square waves.

Okabe et al.[16] as shown in Figure 13. By a statistical argument these studies can shed light on intermittency in several ways. For a sampler synchronized to an independent clock, the response time would have a uniform distribution between the delay time alone and the delay time plus a sampling period. If the sampler is synchronized to the input, an impulse function-type distribution for the delay time is to be expected, and is approached by the experimental graph.

c) *Ramps:* We gave considerable attention to the response of the operator to ramp inputs since the sampling or quantization limitations of the hand control system can be determined by testing with a ramp input if the system acts as a position servo. No physiological basis for a velocity servo was known but we were also interested in finding conditions under

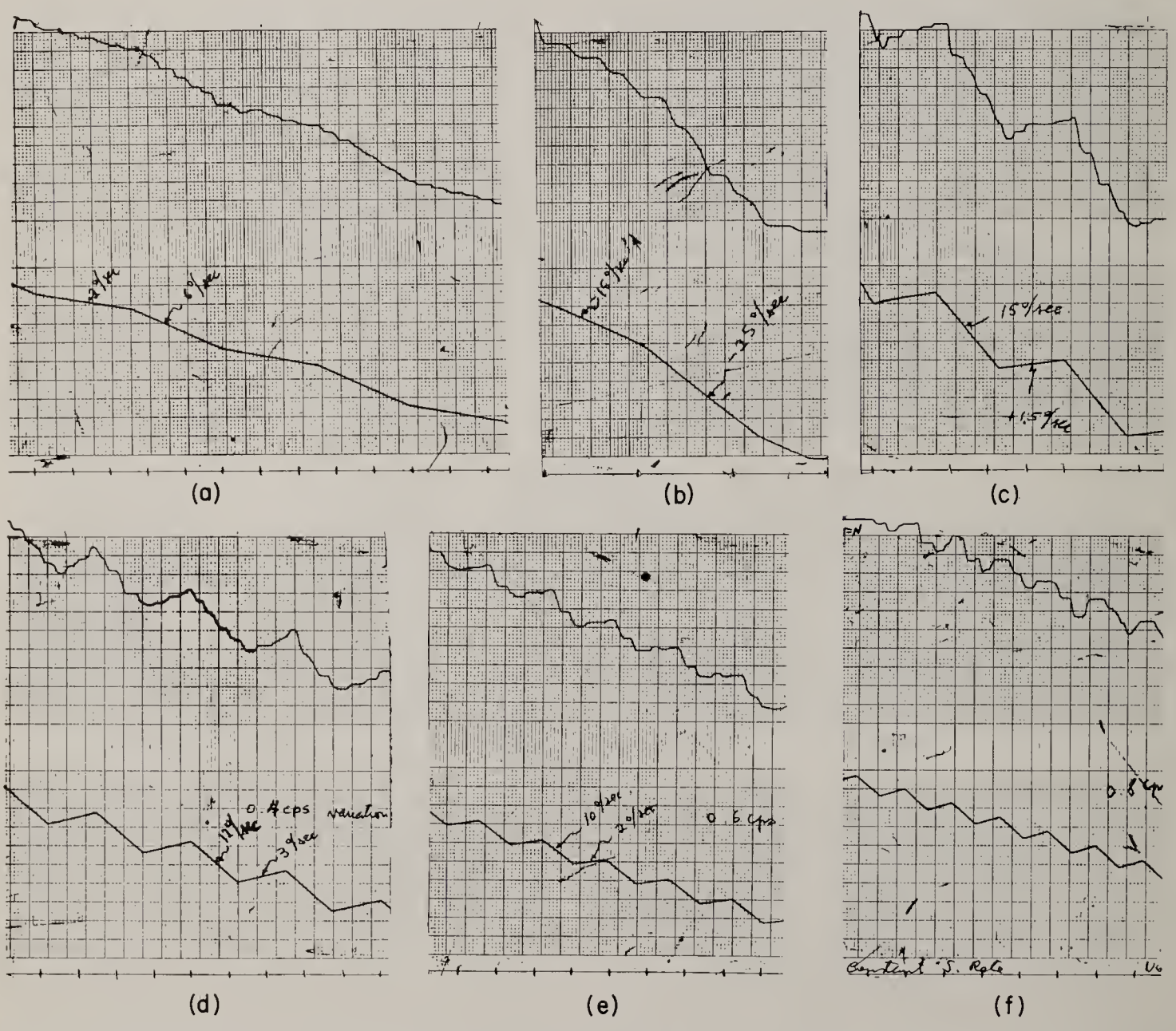
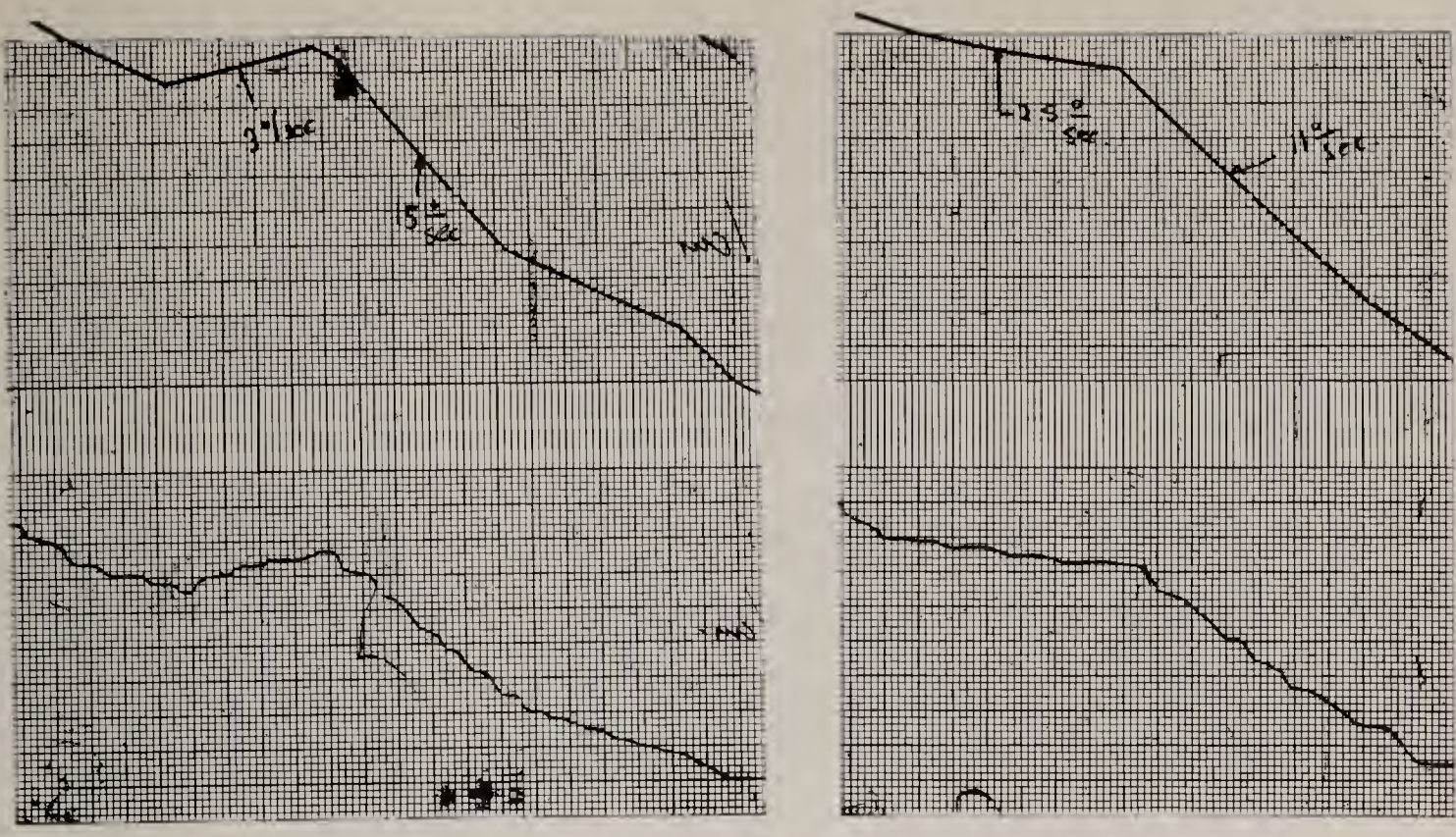
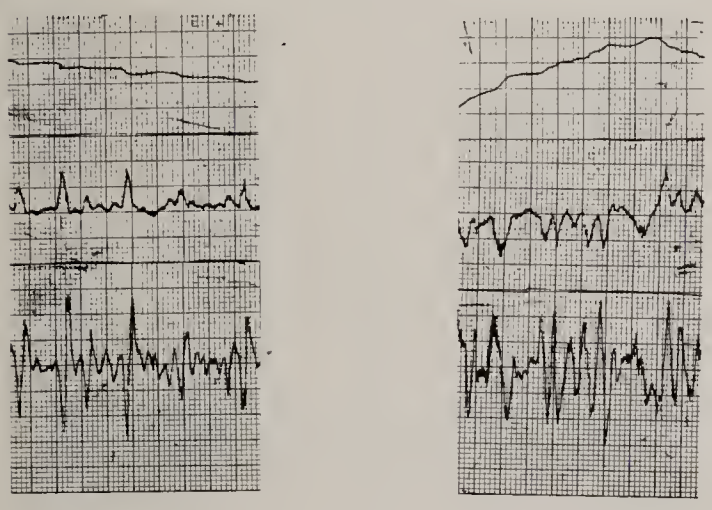


Fig. 14.—Responses to unpredictable ramps, handle loaded with inertia and friction. Abscissa scales show time in seconds.



(a) (b)

Fig. 15.—Responses to unpredictable ramps.



(a) (b)

Fig. 16.—Ramp responses with output velocity and acceleration indicated. Time scale: 200 msec/large division.

which the hand could exhibit velocity servo characteristics. The ramp was presented as part of a more complex combination to avoid prediction. Figures 1, 14 and 15 show inputs and responses to ramps ranging from 1.5° per sec to 25° per sec. Figures 16 and 17 also present velocities and accelerations. The main observation that can be derived from ramp experiments is evidence for sampling-like intermittency. Quantitization or dead zone features are unimportant except for very slow ramps, less than 1° per sec. Other observations include performance deterioration for fast inputs (see Figure 14f), apparently no velocity servo, and very little interpolation between samples, except possibly for some high speed inputs.

Figure 18 shows the quasi-linear rise velocity of the "saccades" as a function of input ramp velocity. Although rise velocity changes with input velocity, this does not correspond to a velocity servo. Rather, saccadic rise velocity is more likely a function of saccade amplitude. Figures 19a and 19b, also derived from ramp responses, show that the size of the saccades is fairly linear with input velocity, and the rate of repetition of saccades is 2.5 cps for most of the input velocity range.

Observation of velocity and acceleration waveforms for ramp responses show that the series of saccades is like a collec-

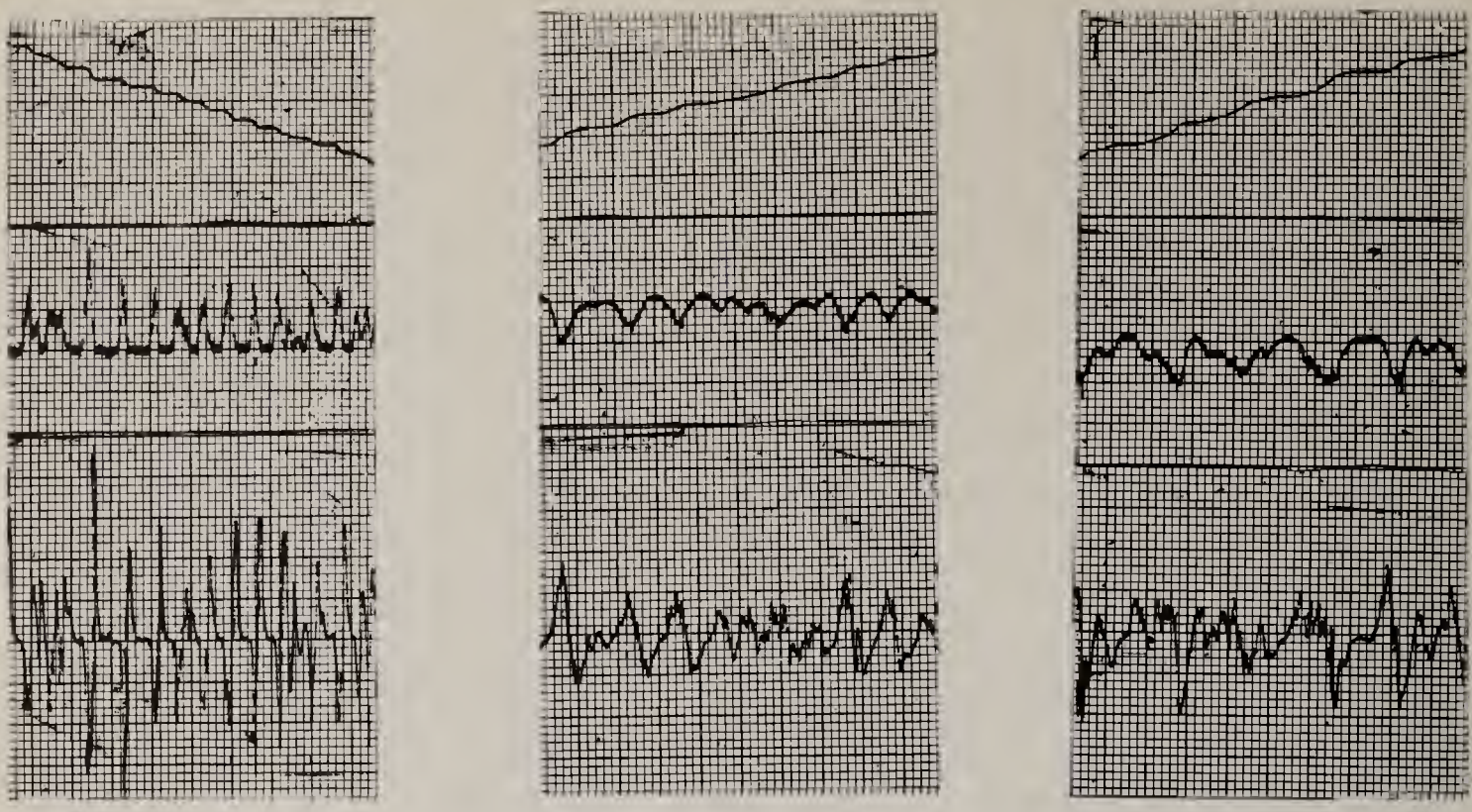


Fig. 17.—Ramp responses with output velocity and acceleration indicated. Loaded handle. Time scale 200 msec/large division.

tion of step responses. Figure 20 illustrates the variation of these saccades from tense to relaxed conditions. Finally, Figure 21 shows responses to predictable ramps for contrast.

Open Loop and Variable Feedback Transients

Open loop experiments are very useful for the analysis of biological servo systems since the models of these systems are not unique and an open loop measurement can show the order of the system and its low frequency behavior more clearly than a closed loop measurement. Variable feedback serves to correlate open loop and closed loop experiments.

Figures 6 and 5b illustrate the experimental method for open loop and variable feedback transients. The display becomes:

$$\theta_d = \theta_i + G\theta_o \qquad (1)$$

where θ_i = input, and θ_d = display. For open loop $G = 1$, and for variable feedback $0 < G < 1$. The error becomes:

$$\theta_e = \theta_d - \theta_o = \frac{G-1}{G}\,\theta_d + \frac{\theta_i}{G} \qquad (2)$$

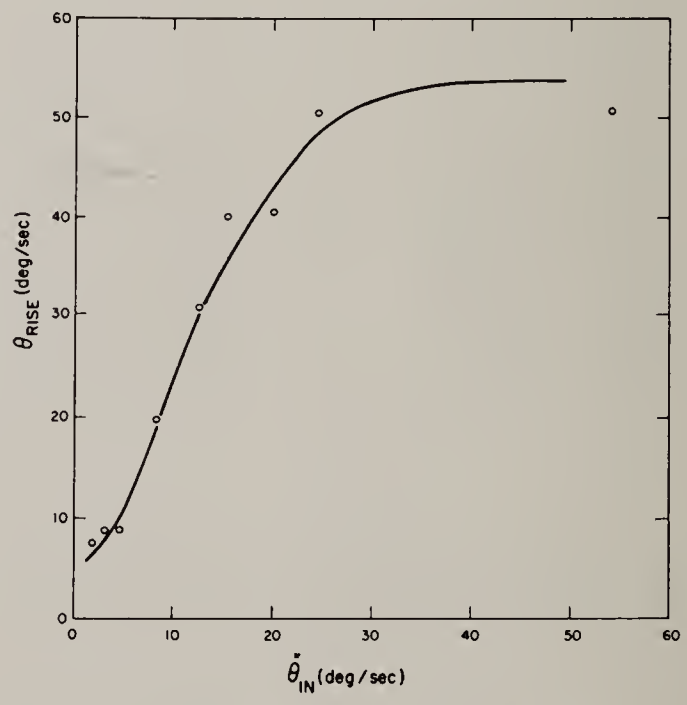
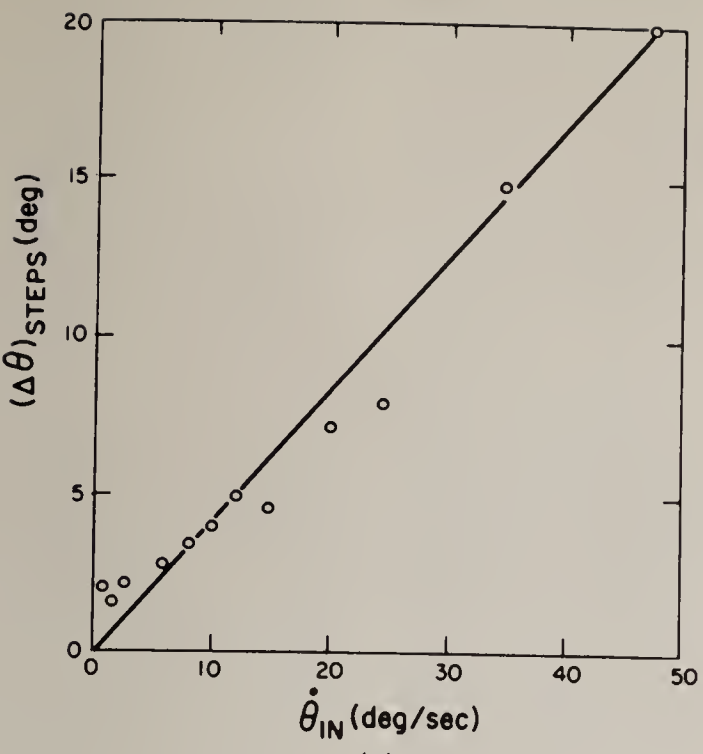


Fig. 18.—Quasi-linear relationship between saccadic rise velocity and input velocity (random ramp input).



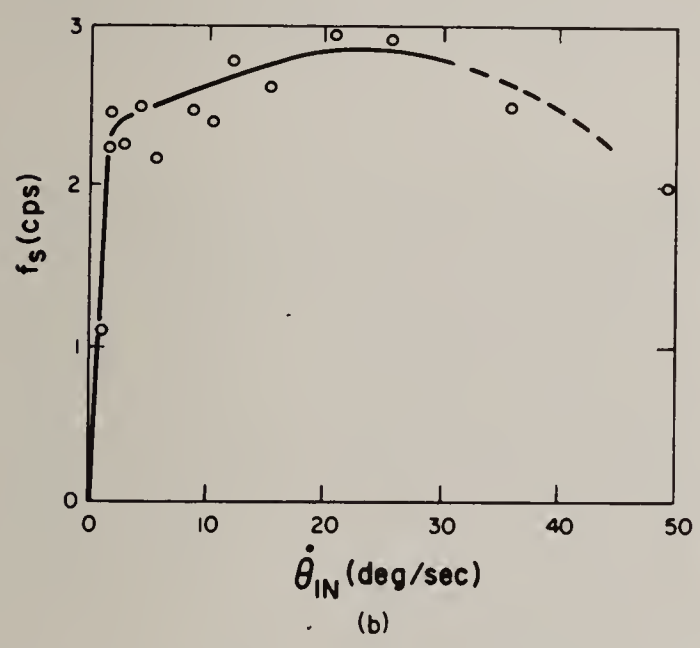


Fig. 19.—(a) Size of intermittent response as a function of input velocity. (b) Frequency of intermittency as a function of input velocity.

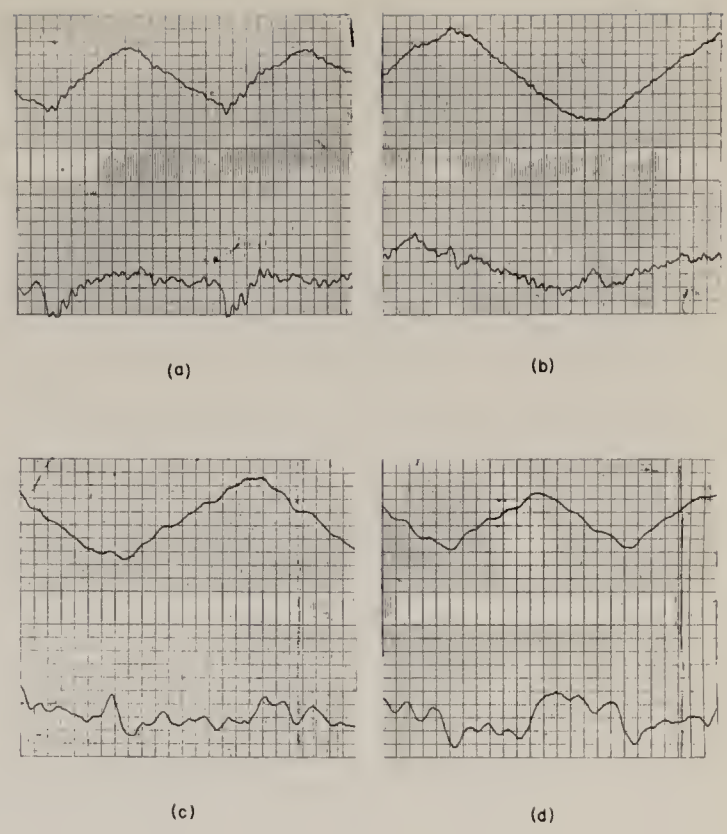


Fig. 20.—Output and error for ramp inputs. Tense conditions (a) and (b); relaxes conditions (c) and (d).

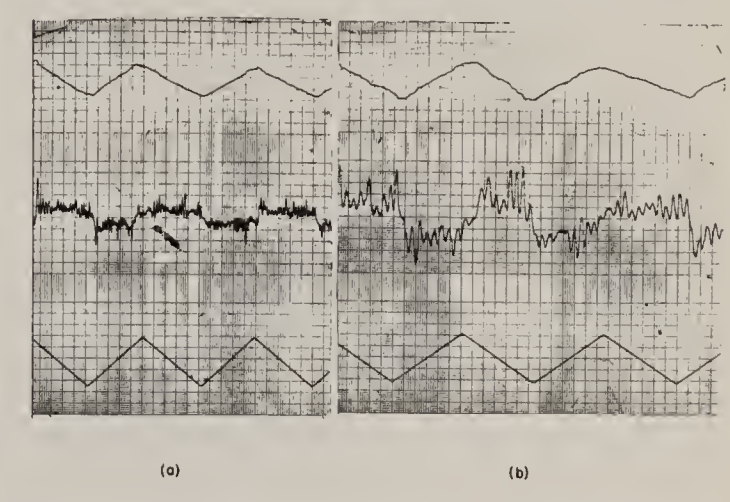
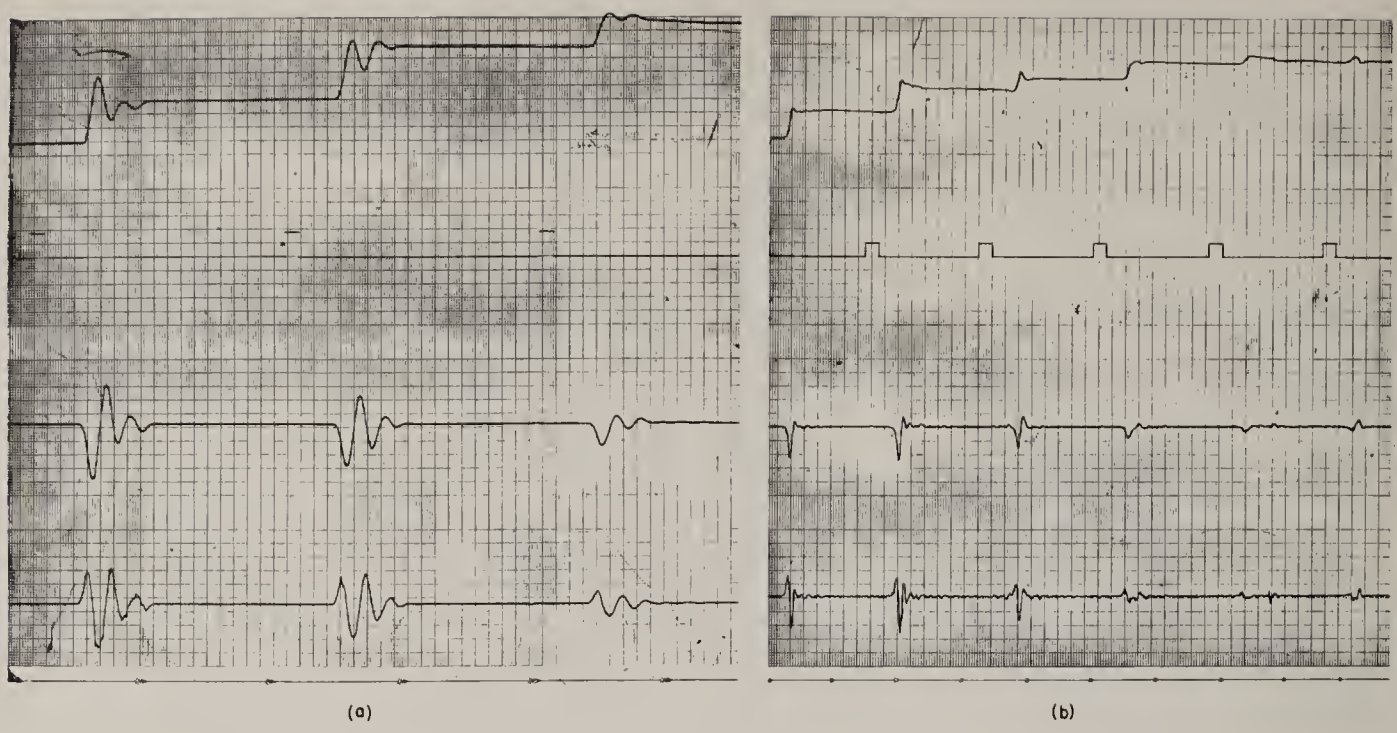


Fig. 21.—Response to known 8°/sec and 16°/sec ramps. Time scales: (a) 1 sec = 2 large divisions (b) 1 sec = 5 large divisions.

Short pulses and steps rather than ramps were the main inputs considered. Figure 22 shows the responses to 100 msec. and 200 msec. pulses. From these experiments we observed that a) the responses were entirely analogous to closed loop step responses; b) the initial corrections were larger than but proportional to pulse size; and c) the final values were related more to pulse area, and were attained after oscillations of the same frequency as in the close loop responses.

The step responses, shown in Figure 23 look like a staircase made of saccades at a rate of 4-5 per second. The ratio of correction to step size is again larger than unity.

Figure 24 is an interesting correlate of these observations. The inputs are repetitive 5 cps and 2 cps positive pulses. The integral of this waveform appears as a ramp to the 3 cps sampler and the response looks like both the open loop step response and the closed loop ramp response.



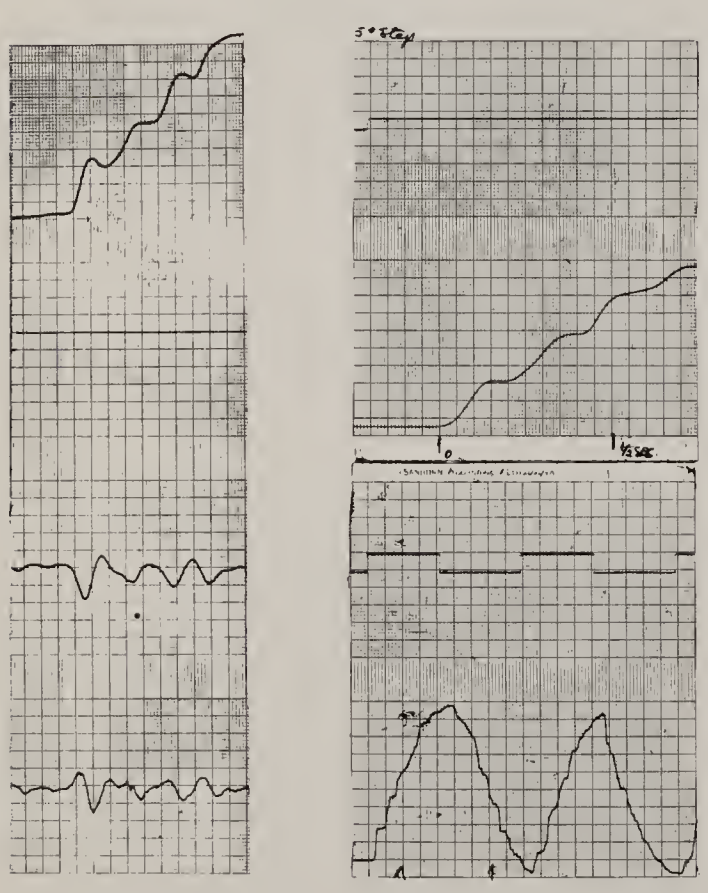
(a) (b)

Fig. 22.—Pulse responses of open loop system. Upper trail output position, next trail minus output velocity, lowest trail output acceleration.

Observations about variable feedback responses, shown in Figure 25 are included in the discussion.

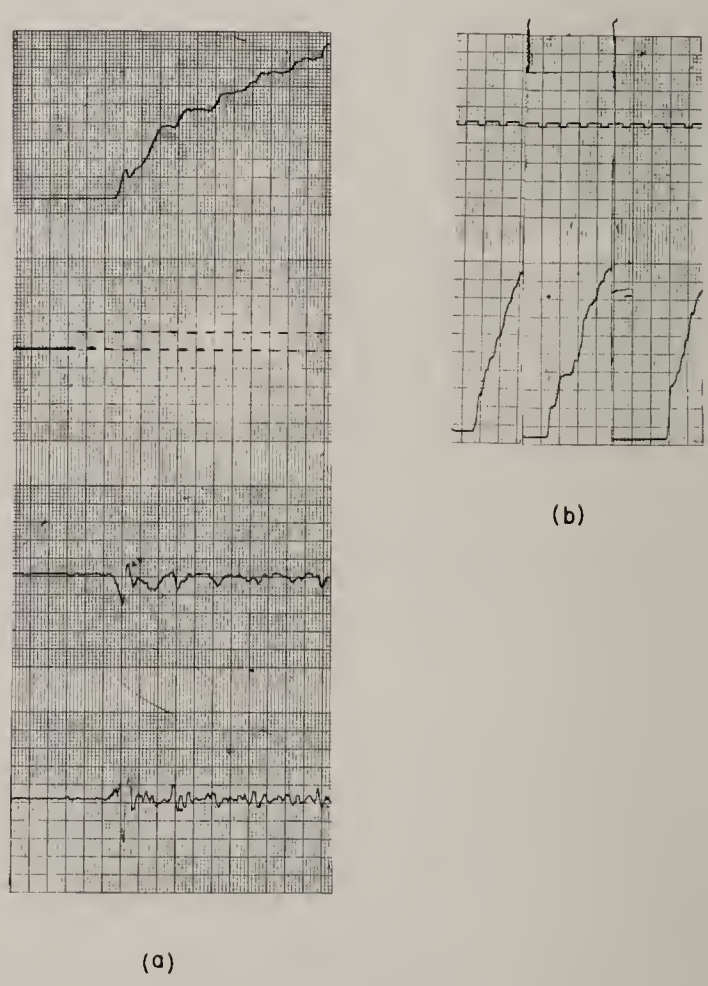
Continuous Random Inputs

As explained previously, the approximations to continuous random inputs



(a) (b)

Fig. 23.—Step responses of open loop system, loaded handle.



(a) (b)

Fig. 24.—Open loop system. Responses to high repetition square waves; analogous to step responses (a) Upper trail output position, next trail input position, next trail minus output velocity, lowest trail output acceleration (b) Upper trail input position, lower trail output position. Time scale: (a) 1 sec = 5 large divisions (b) 1 sec = 1 large division.

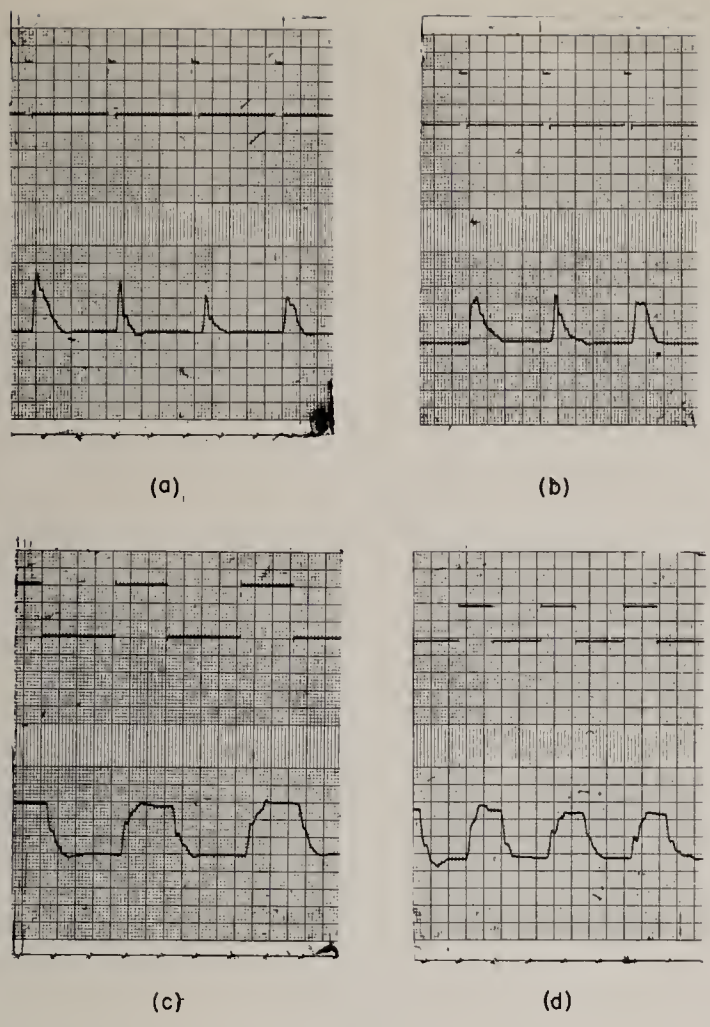


Fig. 25.—(a) Pulse response with G = ½; and (b) pulse response with G = ⅔; (c) step response with G = ½; and (d) step response with G = ⅔. Abscissa scales are time in seconds.

were combinations of five to ten harmonically unrelated sinusoids generated and analyzed by a computer. Short runs (20 sec) were used to avoid operator adjustments shown, by previous investigators (4, 14, 19), to depend on input spectrum.

Figures 26 and 27 show various input spectra and the pertinent averages of gain and phase frequency response. Of the three different frequency responses, that of Figure 27 is of the most interest, probably due to the inclusion of high frequencies. Important characteristics are: peaks in gain and related phenomena in phase around 1.5 cps; decrease in response at high frequencies which can be fitted by a −20 dg/dec line; increase in gain from 0.5 cps up; and low frequency gain equal or less than unity.

Response to Predictable Inputs

In order to obtain a description of performance as a function of frequency, the subjects were asked to track single sinusoids. Magnitude and phase were obtained up to 3 cps. (The subjects then began to act as independent generators.) The experimental points and a fit by transfer function are shown in Figure 28. For this fit to agree with the phase points, an ideal predictor e^{ts} has to be included, an expected phenomenon for these predictable inputs. The transfer function was:

$$F(s) = \frac{{}_e 0.1s}{(1 + 0.13s)(1 + 0.053s)(1 + 0.016s + 0.0028s_2)} \qquad (3)$$

Figures 8e and 12e refer also to predictable inputs, in the time domain. Figure 15 shows the response to known triangular waves; saccades are absent and only 10 cps fluctuations show up. All these phenomena will be considered in the discussion.

DISCUSSION

Features of Model

In this section we will discuss some of the characteristic features of our model, evaluate the model itself, and relate our work to previously published research in this field as well as to other models.

We have postulated a feedback, position control system (Figure 5a) for the hand movement system, and included an intermittency due to alternation between voluntary and reflex control. We will now discuss the various experiments, observations and assumptions.

a) *Feedback system:* Human engineering investigators like Tustin,[19] Elkind,[4] McRuer and Krendel[7,10] have proposed

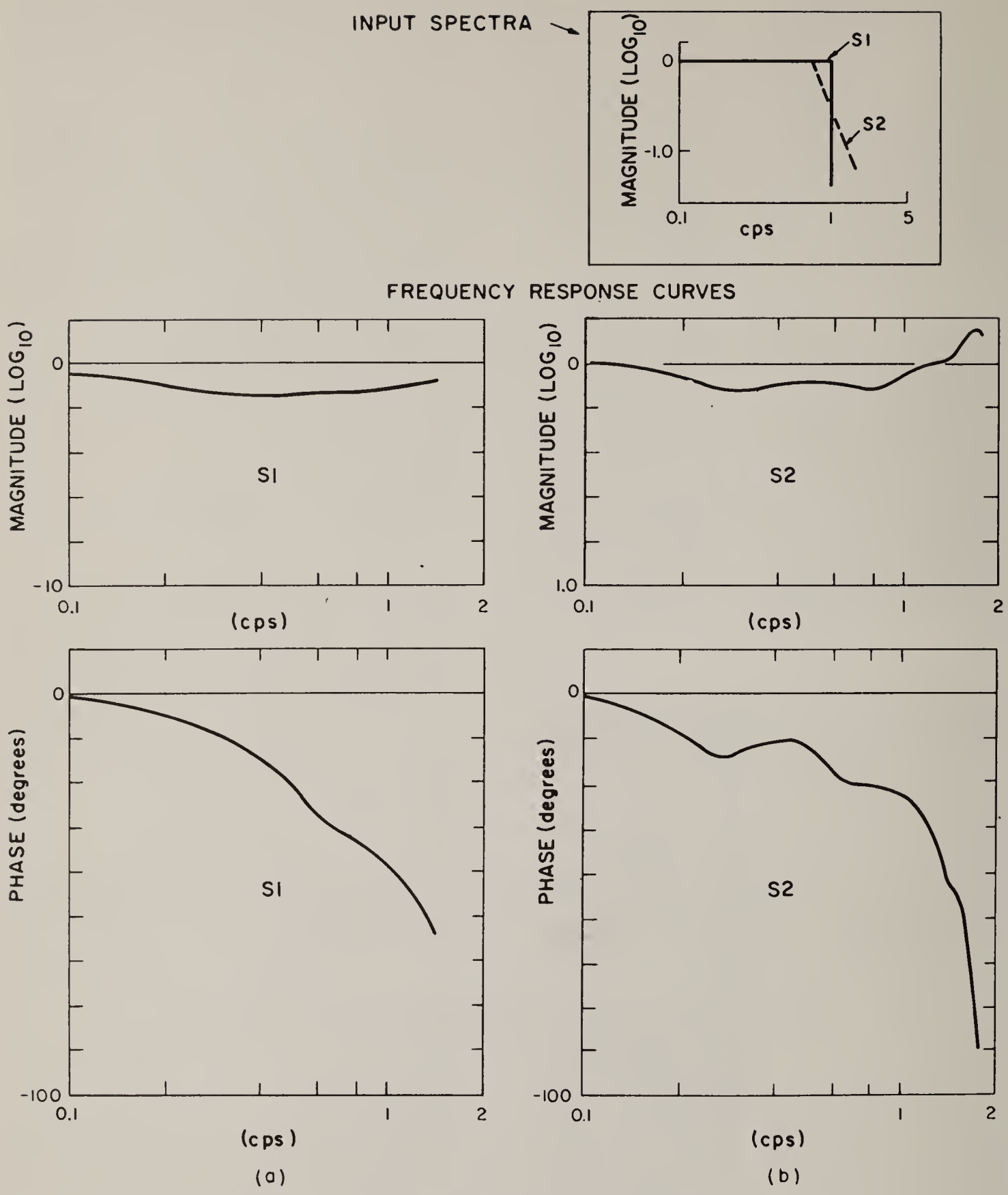


Fig. 26.—Frequency responses to quasi-random continous signals. Input spectrum shown.

feedback systems for the hand control. Indeed, the adequacy of such representation depends upon the ability of the operator to correct for disturbances and to follow a visual input up to his dynamic limits. The human operator can apply several criteria to his tracking such as minimization of disturbance or exact reproduction of the input.

b) *Position servo:* We can explain the topology of the model in terms of the behavior characteristics of the human operator for unpredictable inputs. That the hand system is essentially a position servo is supported by the following arguments:

(i) The final value of the error is zero

for any kind of step input. This requires an integrator in the loop so that if a step (K/s) is applied:

$$\text{Final Value} = \lim_{s \to o} \frac{sK}{s} \frac{1}{1 + H(s)/s} = \lim_{s \to o} \frac{Ks}{s + H(s)} = 0 \qquad (4)$$

(ii) The open loop responses shown in Figures 16, 17, and 18 give evidence of the integrator since a step input produces a (discrete) ramp, and pulse input produces a step output. A discrete ramp results also from fast repetitive steps whose integral, and that of step half as large, are equal, except for a small ripple.

(iii) The ramp experiments show the inability of the subject to follow the input when the ramp was unpredictable; the error did not go to zero. The ramp input (v/s^2) is precisely one order higher than the tracking system.

c) *Velocity:* Velocity servo characteristics are not apparent since very little interpolation appears between saccades, for ramp inputs (Figures 1 and 14–17), and constant velocity sections are infrequent. In addition, very few corrections occur in the direction opposite to that of target when following combinations of ramps. A combination of position and velocity servo could originate such corrections, as happens in the eye tracking system.[17,21] Of striking interest is the inability of the hand servo to smoothly follow an unpredictable ramp. The quasi-linear dependence of θ_{rise} on θ_{in} (Figure 18) should not be confused with the action of a velocity servo.

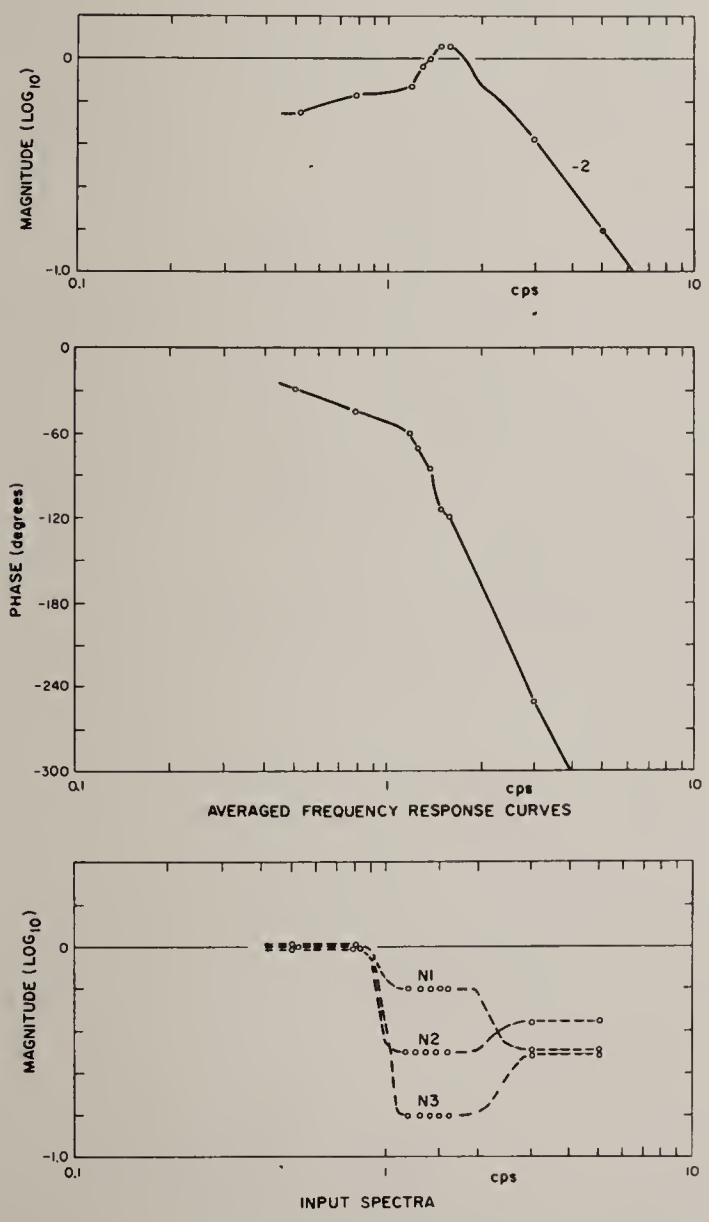


Fig. 27.—Average frequency response to quasi-random continuous signals. Input spectra shown.

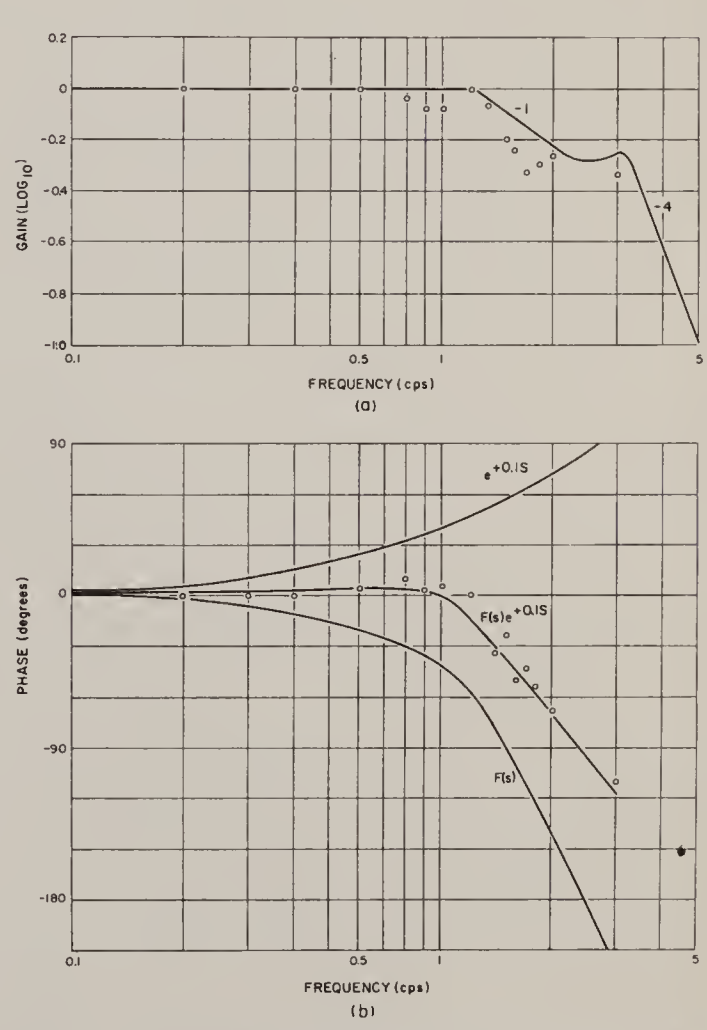


Fig. 28.—Frequency response to closed loop predictable sinusoidal inputs and fit by a transfer function.

d) *Other features:* We will now consider other features of our model, and review previous models. Figure 29 presents references for the discussion of compensatory and pursuit tracking configurations, as well as the models proposed by Bekey[1] and Lemay and Wescott[8] for compensatory tracking, and by Young and Stark[17,21] for eye tracking. Smith and Cortes[2,12] proposed an optimal bang-bang system.

In compensatory tracking, the error is the only information received by the human; conversely, while in pursuit tracking, both input and output are perceived (Figure 29). Since the system is a position control system, thus requiring an integration in the loop, we choose the ideal linear pursuit model shown in Figure 29 as a starting point. In such a model, the actuating signal is:

$$m(t) = \theta_{act} = k_2\theta_i + k_i\int \theta_e dt \tag{5}$$

and

$$e^1(t) = \theta^1 e = \frac{1}{k_1}\frac{dm}{dt} \tag{6}$$

We attribute the operation k_1/s and a delay, T_{d2}, to the central nervous system (see Figure 5a). Although a more complex model including intermittency could be assumed for the delay and dynamics block, we try to use the simplest models for the less known parts of the tracking system; indeed, the integration in the

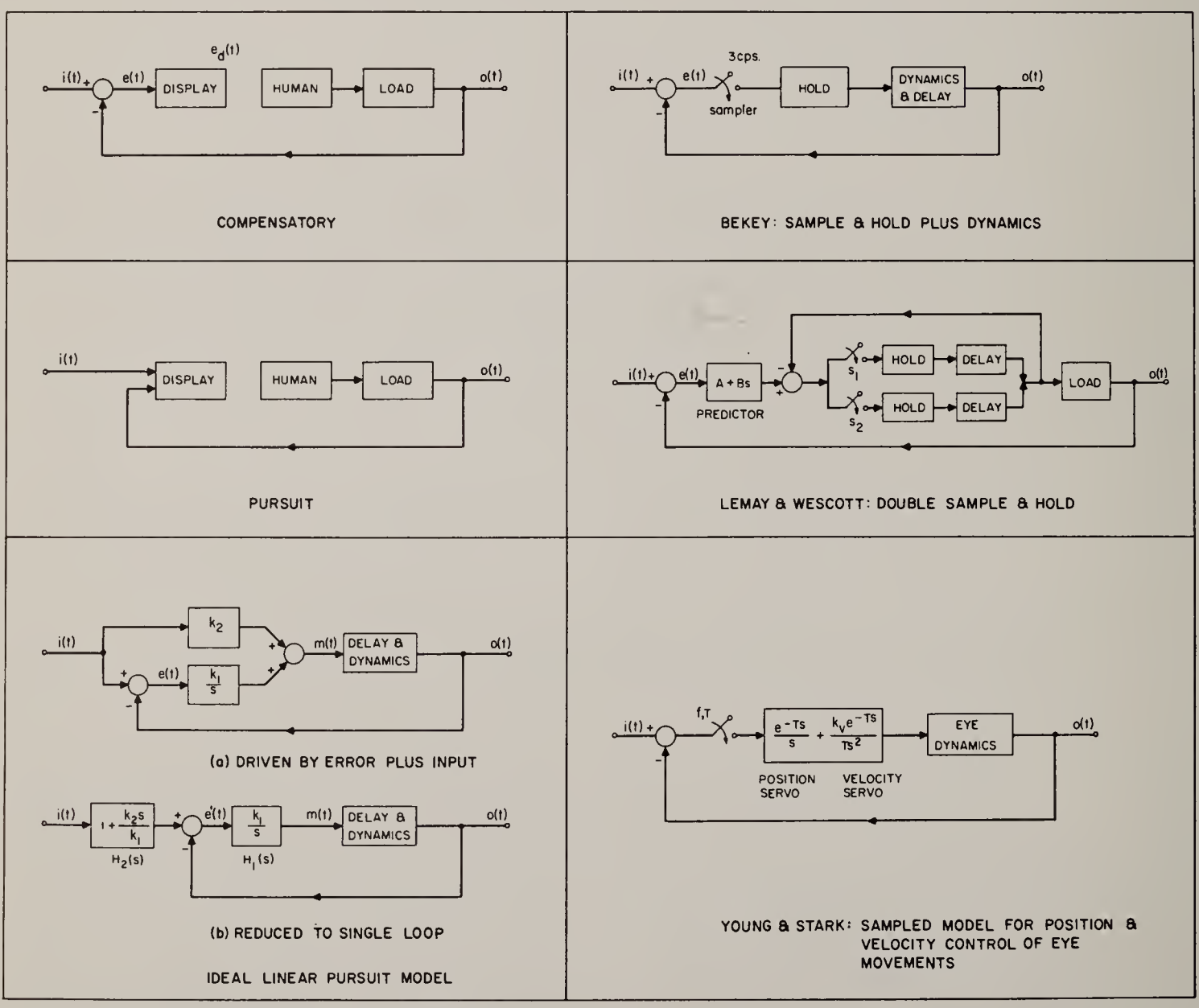


Fig. 29.—Other continuous and discontinuous models for hand tracking.

central nervous system must be discrete in some unknown way. We attribute the delay T_{d1} to perception. The dead zone results from the experimentally verified impossibility of correcting extremely small errors.

The integrator followed by an intermittent element introduces a delay, approximately equal to $T_s/2$ where T_s is the "sampling" period. Taking this and known physiological factors into account, we divide the total response delay as follows:

Visual latencies $= T_{d1}$	$=$ 40 msec
Central nervous system and AMNC intermittency $= T_s/2$ (implicit)	$=$ 165 msec
Conduction time $= T_{d2}$	$=$ 15 msec
Muscular contraction time $= T_{d3}$	$=$ 30 msec
	$=$ 250 msec

The dead zone varies with the individual and with the system. It may have influenced the results for very slow ramps (see Figures 19a and 19b).

Tustin[19] and Elkind[4] obtained fits of the form

$$G(s) = \frac{K_i e^{-0.18s}}{1 + 0.85s} \qquad (6a)$$

for the human operator in compensatory tracking. These were optimum fits in a mean square sense, and this factor and the problem of spectrum selection may

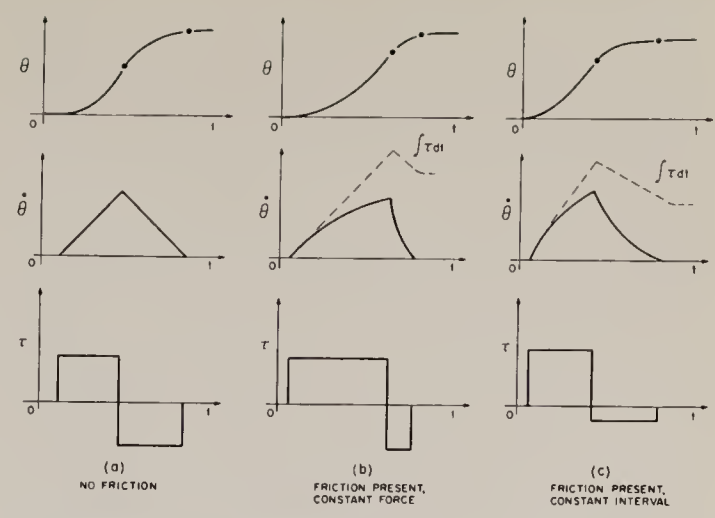


Fig. 30.—Time optimal step responses.

explain the absence of the integrator.[9] Bekey took Elkind's fits and added sampler and hold elements. His compensatory model thus explains the occasional peaks in the frequency response but does not explain the overshoot in the step response, the open loop and variable feedback responses, and the consistent oscillations in the transient responses except for improbable dead time resonances.

Variable Feedback Experiments

We can consider now our variable feedback experiments, ignoring intermittency since, from experimental data, it appears only to add a ripple to most outputs. We will take into account the effects of delay and hand dynamics after obtaining equations which neglect these factors: (see Fig. 5b).

$$\theta_d(s) = \theta_i(s) + G\theta_o(s) \qquad (7)$$

$$\theta_e(s) = \theta_d(s) - \theta_o(s) \qquad (8)$$

$$\theta_o(s) = k_2\theta_d(s) + k_1\theta_e(s)/s \qquad (9)$$

solving:

$$\frac{\theta_o}{\theta_i}(s) = \frac{1}{1 - G} \times \frac{1 + s\,{}^{k_2}/_{k_1}}{1 + \frac{s}{k_1}\frac{1 - k_2G}{1 - G}} \qquad (10)$$

If $G = 1$,

$$\frac{\theta_o}{\theta_i}(s) = \frac{k_1}{s(1 - k_2)}\left(1 + s\frac{k_2}{k_1}\right)^{-} \qquad (11)$$

If $k_2 = {}_o$, but $G = 1$,

$$\frac{\theta_o}{\theta_i}(s) = \frac{k_1}{k_1(1 - G) + s} \qquad (12)$$

If $k_2 = {}_o$, and $G = 1$,

$$\frac{\theta_o}{\theta_i}(s) = \frac{k_1}{s} \qquad (13)$$

If we consider Equation 13, the open loop impulse response is a delayed step with a rise time determined by hand dynamics. The step response is approximately a delayed ramp. We deduce from Equations 12 or 10 that the effect of nonunity external feedback is that the step response goes to a final value $1/(1 - G)$, and the impulse response dies out fast for small G and very slowly as G approaches unity.

If we look at Equations 10 and 11, we see that the effect of k_2 is to increase initial values by correcting delays, and to increase final values by $1/(1 - k_2)$.

If $G < 1$ and $k_2 > 0$, we can expect step responses to have an initial jump of the order of $k_2/(1 - k_2G)$ and a higher final value $1/(1 - G)$. The short pulse response should die out at a high rate if G is small. Open loop experiments show that the size of the correction is generally larger than the size of the step; this observation agrees with our assumption of $k_2 \neq 0$ in Equation 5.

Variable feedback experiments, shown in Figure 25, illustrate that for pulse inputs the initial jump is independent of G, as was to be expected, and the decay rate is slightly faster for $G = 1/2$ than for $G = 2/3$, as expected. For step inputs the final value is higher than the initial value, and higher for $G = 2/3$, than for $G = 1/2$, although not as high as expected.

We have shown that our general topology and assumption of a position control system is consistent with all unpredictable transient results. Indeed our model is similar to Young and Stark's model of the eye system, which applies to a situation similar to compensatory hand tracking ($k_2 = 0$), and which differs from the hand system in the dynamics, and in the location and type of intermittency.

Prediction Operator

Before explaining the contributions of Smith and Cortes, and Lemay and Westcott, we recall the importance of the distinction between unpredictable and predictable tracking (13, 17).

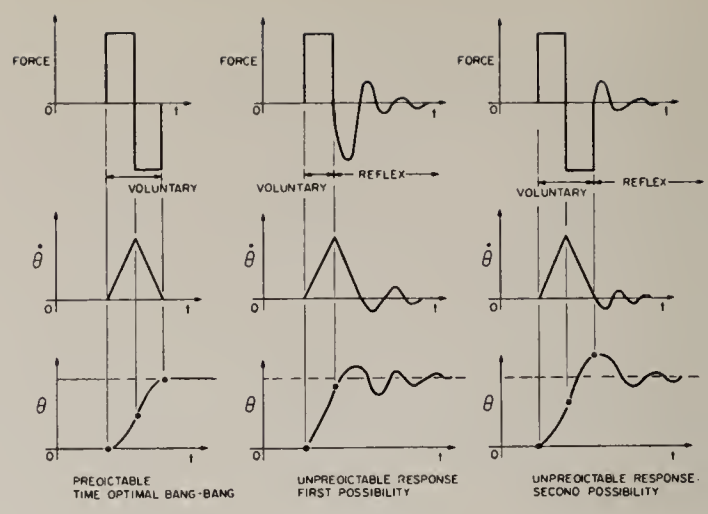


Fig. 31.—Possible types of ballistic movements.

a) Comparison of Figures 26 and 27 with Figure 28 shows, both in magnitude and phase, the greater ability of the subject to track continuous predictable signals. Furthermore no peaking occurs at 1.5 cps.

b) Figure 21 shows that if ramps are predictable the subject can follow them without 3 cps intermittency and with apparent velocity servo characteristics.

c) Figures 8 and 12 show clear improvement in the subject's performance when the step and pulse inputs are known beforehand.

d) Response times are reduced for predictable steps (16) (Figure 13).

e) The hand system can perform very rapid and complex voluntary tasks, while it cannot follow simple unknown signals of frequencies higher than 3 or 4 cps.

When the signal is not entirely unpredictable, a whole range of intermediate situations can occur. The importance of considering unpredictable signals is also due to the uniqueness of the unpredictable model, and to the large variety of predictable models as the input and learning conditions change.

Frequency Response for Unpredictable Inputs

We must speak finally about frequency response for unpredictable inputs. On the basis of analytical and experimental work done at the Neurology Section at Massachusetts Institute of Technology,

very approximate theoretical frequency response characteristics can be obtained. However, no simulation of the total model response has yet been done.

Using average values from typical tracking situations we have computed

$$\alpha = 10^{-3} \tag{13a}$$

and

$$\frac{\theta}{T}(s) = \frac{10^{-4}}{s(1 + 0.56s)} \tag{13b}$$

The magnitude characteristics of the spindle and load are shown in Figure 34. The gain of the proprioceptor loop is obtained by standard servo approximations. For example, we have closed the loop with a phase margin of only 30°. This is reasonable since we have already observed the low damping of the oscillations in between corrective movements. In considering the visually open loop we have omitted the intermittency but added a peak at 1.5 cps, as shown in Figure 35. The loop has then been closed with typical phase margins of 45° and 70°. The effect of the $(1 + k_2 s/k_1)$ term is included as a prefilter which is operative only from .5 to 2.5 cps, since at high frequency the operator has only the error to rely upon if he is to follow at all. This approximate prediction of total gain is in agreement with the experimental graphs of Figure 27. However, simulation should be carried out, since an exact analysis of our model is too difficult. It would also be interesting to look at the impulse responses with reference to the above approximations.

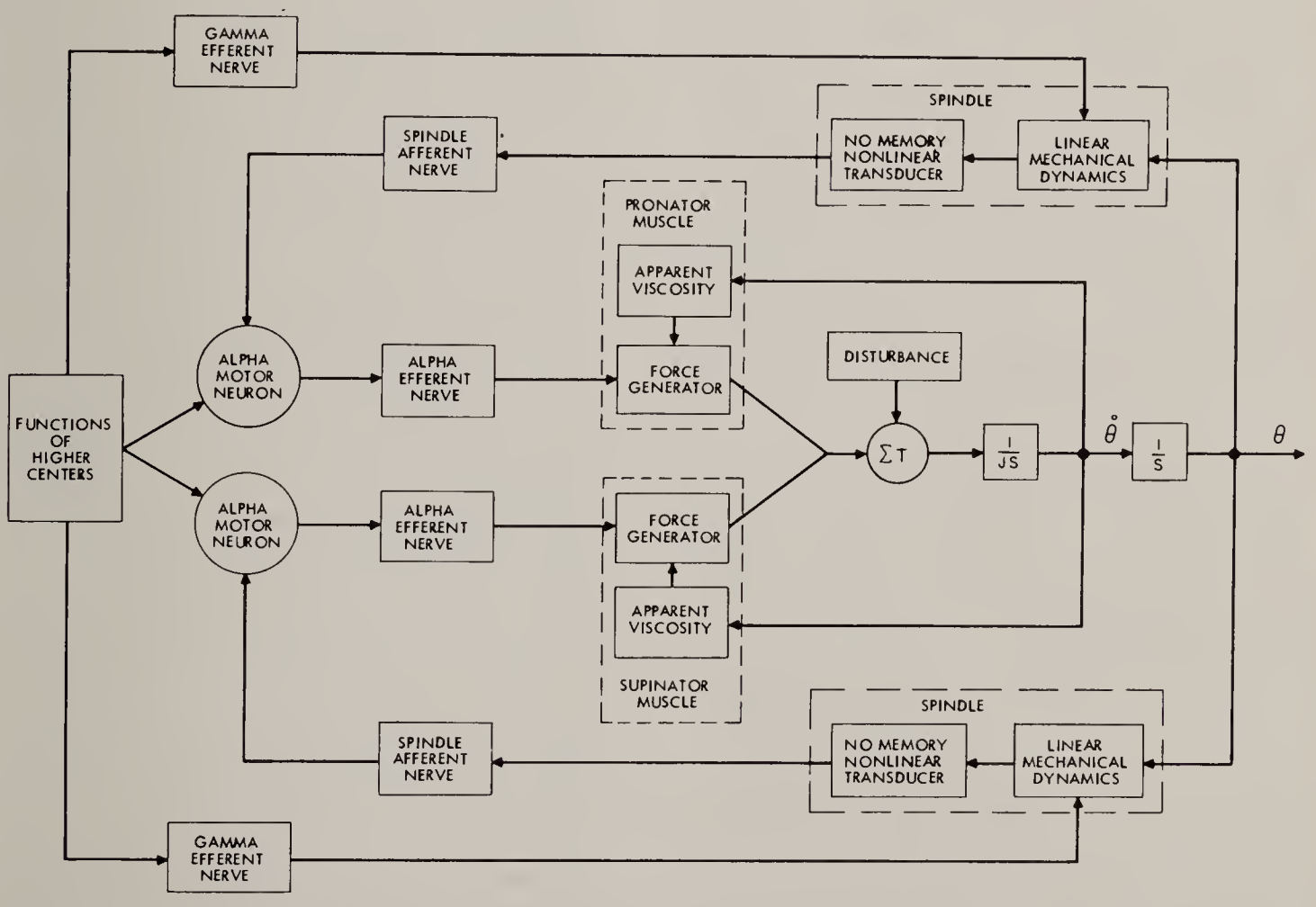


Fig. 32.—Motor coordination system.

Step Response

Smith and Cortes made an extensive study of the step response with various large inertia loads and postulated a "bang-bang" model for the human operator, which was optimal for constant force (see Figure 30a and 30b). Lemay and Westcott started from step response and presented a model (Figure 29) which included a representation of the arm dynamics as a pure inertia, and a system of samplers for production of a pre-programmed time-optional step response for constant interval and adjustable force (see Figure 30c). The predictor was added in order to improve the model's fit to experimental random signal responses, although it would have been more logically added to the model for the known step inputs. The use of constant force instead of constant interval in the time-optimal model introduces only small errors if the inertia load is large; however, our step responses with velocity and acceleration measured—particularly Figure 12—show a response similar to time-optimal (Figure 31) for the predictable case, but different for the unpredictable case: Figure 31 (center) indicates one possible type of action, but Figure 31 (right) has to be considered as an equally likely possibility. As we shall discuss, physiological data up to now support either of these two modes of response, while we claim the time optimal "bang-bang" model to be valid only for predictable steps.

Intermittency and Psychology

Telford and later investigators[3,5,6,9] have studied and described discontinuity in the operation of physiological systems which, like the hand control system, require a stimulus to be perceived before a response is elicited. A "refractory" period between responses has been observed and measured (0.2 to 0.5 sec), and exceptions to it, as well as effect of training, grouping of stimuli, etc., have been noted by these and other investigators. Most of their experiments referred to discrete stimuli, but Craik[3] and Bekey[1] have studied the extension to continuous stimuli. Ward, Bekey, and Lemay and Westcott have proposed sampled data models of the human tracker. Other investigators have questioned the presence of a sampler here. The hand sampler is not as clear as in the eye system both because of the greater use of prediction in hand tracking, and because of the considerable inertia of the hand which tends to smooth out neurological intermittency.

Our experiments suggest that intermittency is present for unpredictable inputs, but both our results and physiological considerations suggest it to be irregular and asynchronous. The experimental evidence such as the unpredictable ramp studies and the frequency responses such as those shown in Figure 27 are prime sources of behavioral evidence for the intermittency. We have noted deterioration of performance such as is shown in Figure 14 when the frequency of a repetitive signal exceeds 1.5 cps. A crucial experiment supporting the existence of intermittency is the refractory period of about 250 msec in short pulse responses. Open loop and variable feedback responses also show intermittent corrections which are generally faster (about 4 per sec). The distribution of delays approaches that of an input-synchronized sampled system. Some of the frequency response experiments (Figure 27) show peaks in the gain and related phenomena in the phase around 1.5 cps, which can be interpreted as half a sampling frequency.

The impulse responses do not show intermittency. Indeed the sampling rate is not constant, as is shown by the absence of peaks for most of the spectra used by Bekey. Another explanation might be that the presence of another loop—the proprioceptive loop—obscures the phenomena. With regard to our models for unpredictable step responses (Figure 31), the postulated intermittency means that corrective voluntary control can be applied only for small intervals of time separated by refractory periods.

Reflex control is the only operative one between these periods of voluntary control.

With the postulated type of intermittency, the system is not equivalent to an error sampled system either for the visual or proprioceptive loop. There is always a drive applied to the muscle dynamics. The signals applied to the muscle include new signals generated by the intermittent process, but they also contain signals from the direct input which explains the diminishing but nonzero ability to track past 1.5 cps.

Although a dead zone could be another explanation for intermittency, we believe the above evidence supports a sampling-like type of intermittency. The sampled data experiments are rather convincing on the basis of the prolonged pulse response, the peak in frequency response, and the irregular positional corrections for slow ramps.[11] The present results are especially relevant to the problem of eye and hand interaction. It has been firmly established that the response to unpredictable inputs by the eye tracking control system can be well predicted by a sampled data model.[21,22] However, such phenomena as the irregular multiple step responses to a slow ramp are independent of visual tracking. Further, the sampled data control system for the eye appears to be both position and velocity control while the manual tracking sampled data seems to be only a position control system, thus indicating rather different origins of the control signals to these two complex motor outputs.

One point of interest is the distribution of response times for hand tracking of unpredictable targets; a narrow quasi-gaussian distribution with a mean of 0.24 sec. as shown in Figure 13. This indicates that the sampling times are not clock driven, but rather input-synchronized; with some random deviations from mean response time.[11] If they were clock-driven, one would expect a square distribution from one sampling time to two sampling times with perhaps some additional random variation around this square distribution. The clock-driven distribution predicted by Lemay and Westcott[8] is clearly not found under our experimental conditions.

Physiological Basis of the Hand Control System

A model of the motor coordination system, particularized to the motion of the supinator and pronator muscles of the forearm, is shown in Figure 32. The visual loop and the external input are not included.

The pair of muscles, supinator and pronator, is required to rotate the wrist because of the inability of muscles to push; therefore only one muscle at a time actively aids movement (although the antagonist may be actively braking). The arm load is represented as an inertia, but some force is required to overcome the nonlinear apparent viscosity of the muscle is included.

a) *Actuating elements:* The actuating elements are the force generators which control the contraction of the bundles of muscular fibers called motor units. For maximal excitation all motor units (of the order of 10^4) are fired. We call excitation coefficient (α), that fraction of the muscular cross-sectional area that is activated. Thus, the applied torque becomes αT_{MAX}. The excitation of the muscle is determined by signals sent from the alpha motor neuron by means of the alpha efferent nerve. These signals originate in the cerebrum, cerebellum, and spinal cord. The alpha motor neuron also receives spindle signals transmitted by the alpha afferent nerve; these signals depend on the length of the pertinent muscle. Other higher center signals come to the spindle through the gamma efferent nerve to control the myotatic or stretch reflex.

The dynamic characteristics of muscles have been studied by Houk and Stark at Massachusetts Institute of Technology.[13] The apparent viscosity has been found to be nonlinear and higher for lengthening than for shortening, thus allowing for quicker damping than by a symmetrical element. The arm muscles can be represented as a linearized block:

$$\frac{\theta}{\alpha}(s) = T_{MAX}/s(\beta + \mathcal{J}s) \tag{13c}$$

where β depends on α.

b) *Spindle:* The spindle is a position feedback element connected in mechanical parallel to the muscle. The spindle afferent nerve is connected to a nuclear bag in the center of the spindle. The gamma efferent nerve can contract the spindle fibers, and acts as a level setter. Changes in length or in gamma bias, after being modified by the mechanical dynamics of the tendon, fibers, and nuclear bag, produce contractions in the nuclear bag fibers. These contractions then generate nervous signals which are transmitted to the alpha motor neuron by the spindle afferent nerve. The spindle is highly nonlinear, but the following approximate transfer function has been obtained by Houk for small signals:[13]

$$\frac{\alpha_s(s)}{\theta_d(s)} = \frac{k_s(1 + s/6.8)}{(1 + s/18)(1 + s/200)} \tag{14}$$

The differential behavior over a band of frequencies explains the role of the spindle in the damping of fast movements.

The stretch reflex operates as follows: When a limb is disturbed out of equilibrium, the spindle is stretched and the number of pulses/sec. sent to the alpha motor neuron is increased. The alpha efferent signal from the alpha motor neuron changes and causes the muscle to move the arm back to equilibrium.

c) *Role of the proprioceptive loop:* In the model presentation an alternation between voluntary and reflex control of the alpha efferent pathway, the final common pathway, was postulated. The behavior of the motor coordination system would occur as follows: Voluntary movements are preprogrammed in the higher centers and signaled as a whole. At the time of command release (Position 1, Figures 5 and 33a) spindle efferent control is reduced and higher control of

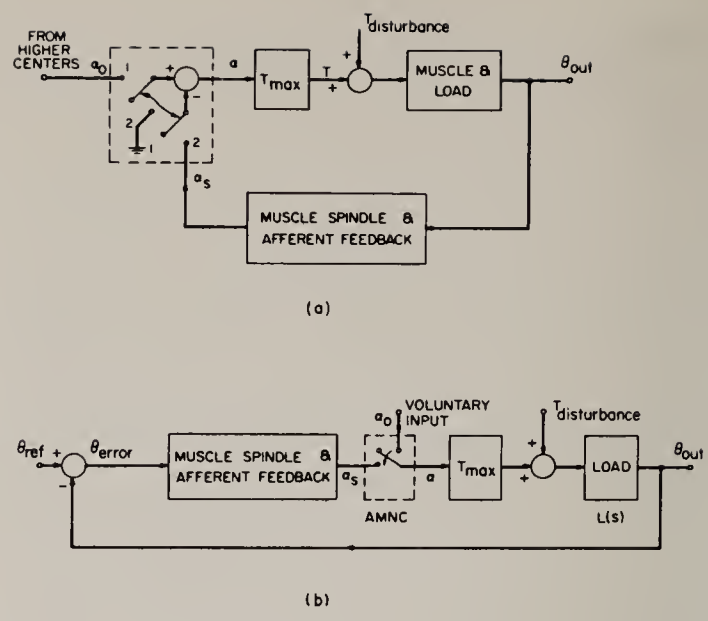


Fig. 33.—Role of AMNC in tracking: (a) original model; and (b) alternate version. "Muscle and load" in (a) represented by L(s) and "muscle spindle and apparent feedback" in both (a) and (b) represented by F(s) in equations 15 & 16.

the alpha efferents is fully turned on. The system is operating proprioceptively open loop, characterized by high gain, low damping and possible postural drift, during a short period of time of the order of 100 msec. Only apparent viscosity opposes motion; however, regulation comes from proprioceptive feedback and from the apparent viscosity.

After the motion has been substantially completed, the spindle afferent control of the alpha efferent pathway is fully turned on and the gamma efferent may be altered for a new set point which corresponds to position 2 in Figures 5a and 33a. The arm may oscillate for a time and is finally clamped to a new position. The new position remains stationary for approximately 230 msec.

If there is still some error, a new correction is applied and the process repeats itself at a rate of some 3 corrections per second. Figure 33b shows an alternate model for the action of the alpha motor neuron system which shows the clamping operation to a new value of θ_{ref}. The following figures of merit can be defined:

$$F_{vol}(s) = \frac{\alpha_o(s)}{\theta_e(s)} = F(s) + \frac{1}{T_{MAX}L(s)} \tag{15}$$

$$F_{dist}(s) = \frac{T\text{—}(s)}{\theta_e(s)} = F(s)T_{MAX} + \frac{1}{L(s)} \tag{16}$$

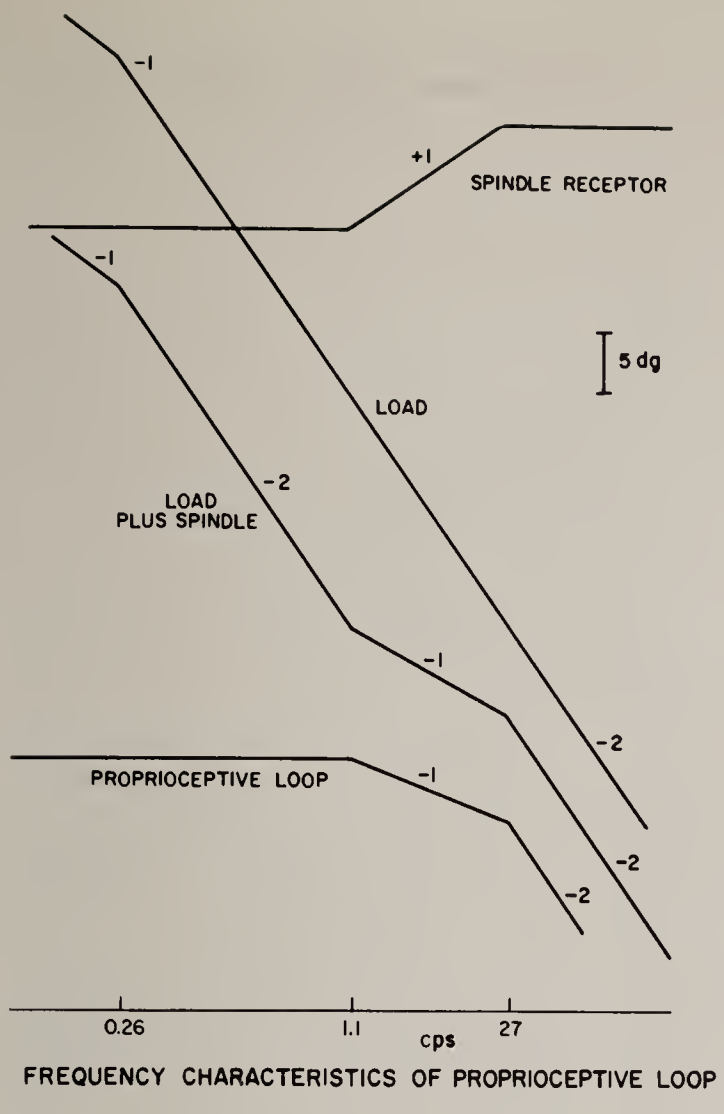


Fig. 34.—Frequency characteristics of proprioceptive loop model.

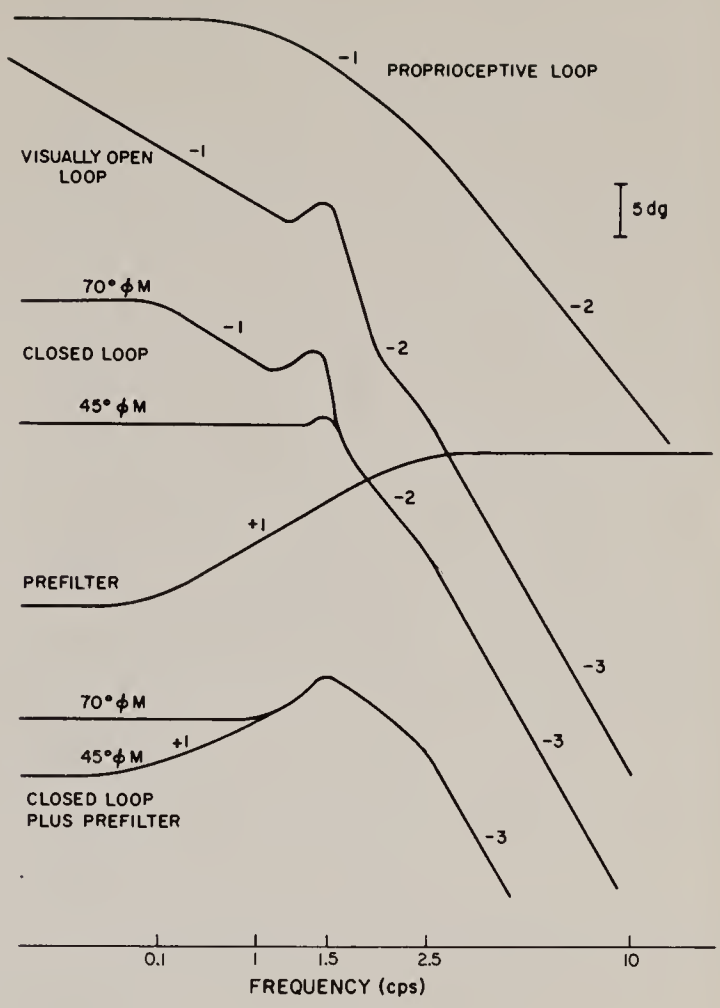


Fig. 35.—Frequency characteristics of the complete unpredictable tracking system model.

High $F(s)$ means low direct gain and little stability. Low $L(s)$ means low gain.

This explanation is supported by considerable evidence. For example, the standard finger pointing and finger-nose-finger tests used by neurologists show the open loop nature of rapid movements. Further, lack of antagonist tone during rapid voluntary "freewheeling" movements favors proprioceptive open loop type of control and suggests that the stretch reflex is inoperative during the rapid portion of these movements.

Oscillations up to a few cps are possible, and the frequency of oscillation is lower if the subject has to correct for disturbances and the proprioceptive loop is closed.[13,14]

In Parkinson's disease the spindle afferent path cannot be easily switched off, and the corticospinal input is thus weakened. Results are rigidity, inability to track, and low freewheeling frequency.[13]

In experiments performed by Stark and Rushworth,[13] the gamma input was blocked with procaine. It was found that the initial part of skillful movements (alpha controlled) was still correct, but the termination was severely affected; the subject lost control of his final arm position or of the termination of paper tracing because the proprioceptive feedback path was inoperative for clamping and damping.

Considerations of transient responses, particularly steps (Figures 12 and 31) also support this dual mode behavior.

CONCLUSION

The major conclusions from our studies are summarized in the model presented. The loading impedance of the arm lies mainly in the inertia of the limb (which

we attempted to minimize with the wrist rotation movement studied), and in the apparent viscosity of the actively shortening and lengthening agonist-antagonist muscle pair. On the input side, the predictor operator yields extraordinarily quick input adaptive recognition of repetitive signal characteristics and requires random or pseudorandom input signals to counteract this factor. The dual control of hand movement requires a continual switching process from postural to voluntary systems, which thus determines which of the two modes has control of the final common path, the alpha motor neuron. This phenomenon provides the intermittency or sampling type of behavior for the hand control system. Experiments on reaction time distribution functions to random steps clearly show that the sampling is input-synchronized, with some statistical spread, and not clock-synchronized as in usual engineering sampled data systems.

The transient experiments demonstrate the refractory period in terms of the minimum-width pulse response to an impulse input. Also, the random ramp inputs show the intermittent steps of response, which vary in amplitude, but not in time interval, with variations in input ramp velocity. This latter experiment also demonstrates the position controller acting alone without a velocity controller, in contrast to the eye tracking system which has both position and velocity control under similar circumstances. Further evidence for the integrator, acting in the position controller, is seen in experiments under open loop and variable feedback conditions. Here the response to a train of pulses is a sequence of steps. Again in contrast to eye movement tracking, the hand system can ordinarily adapt to this bizarre change in the experimental arrangement although an adaptation is not always possible.

The frequency response experiments show different results for predictable and random signals, and illustration of the input adaptive characteristics. The deterministic signals show the hand to behave like a stable second order system with an ideal predictor. Unpredictable signals show evidence for the sampled-data peak, provided, of course, that care is taken in selecting proper input spectra. The quantitative model in addition to intermittency, the integrator, time delays, a minor proprioceptive loop, and plant dynamics, has a lead phase advance operator.

SUMMARY

A hand control model is proposed. Investigation of the hand's intermittency synchronization shows it corresponds to an input-synchronized sampler rather than the clock-synchronized sampler more typical of engineering systems. The velocity control mechanism, similar to that in an eye tracking system is shown to be absent in the hand. A quantitative transfer function for predictable inputs serves further to define the hand's input adaptive characteristics. Stability margin adjustments of a linear reduced model enabled us to match the available quantitative data. The most exciting result of this study is the evidence for intermittency: a refractory period shown in the short pulse experiment, peaks in the frequency response experiments, and a saccadic sequence of steps in response to an open loop step input. □

REFERENCES

1. Bekey, G. A.: The Human Operator as a Sampled Data System. IRE Trans Hum. Factors Electronics, 3:43, 1962.

2. Cortes, A.: The Human Servo: Arm Control. Masters Thesis. Univ. Calif. Engineering Library, Berkeley, 1958.

3. Craik, K. J. W.: Theory of the Human Operator in Control Systems. Brit. J. Psychol., 38:56-61, 1947 and 38:142-148, 1947.
4. Elkind, J. I.: Characteristics of Simple Manual Control Systems. Technical Report, Lincoln Laboratory, Lincoln, Mass., 11, 1956.
5. Halliday, A. M., Kerr, M., and Elithson, A.: Grouping of Stimuli and Apparent Exceptions to the Psychological Refractory Period. J. Exper. Psych., 7:72-89, 1960.
6. Hick, W. E.: Discontinuous Functioning of the Human Operator in Pursuit Tasks. Quart. J. Exp. Psychol., 1:36-57, 1948.
7. Krendel, E. S., and McRuer, D. T.: A Servomechanisms Approach to Skill Development. J. Franklin Inst., 269:24, 1960.
8. Lemay, L. P. and Westcott, J. H.: The Simulation of Human Operator Tracking Using an Intermittent Model. Presented at International Congress on Human Factors in Electronics, Long Beach, Calif., 1962.
9. Licklider, J. C. R.: Quasi-linear Operator Models in the Study of Manual Tracking. Developments in Mathematical Psychol., Luce, R. D., ed., Free Press, 1960.
10. McRuer, D. T. and Kendel, E. S.: The Human Operator as a Servo-system Element. J. Franklin Inst., 267:381-511, 1959.
11. Navas, F.: Sampling or Quantitization in the Human Tracking System. Masters Thesis, Department of Electrical Engineering, M.I.T., 1963.
12. Smith, O. J.: Nonlinear Computations in the Human Controller. IRE, Trans. Biomed. Elect., 11:125-129, 1962.
13. Stark, L.: Neurological Feedback Control Systems: Physiological Models and Behavioral Characteristics of the Adaptive Human Motor Coordination System. Advances in Bioeng., 1, 1966; and Stark, L.: Neurological Servomechanisms: Readings in Bioengineering. (manuscript in preparation).
14. Stark, L., Iida M., and Willis, P. A.: Dynamic Characteristics of the Motor Coordination System in Man. Biophys. J., 1:279, 1961.
15. Stark, L., Okabe, Y., and Willis, P. A.: Sampled Data Properties of the Human Motor Coordination System. Quart. Prog. Rep., M.I.T., 67:220-223, 1962.
16. Stark, L., Payne, R., and Okabe, Y.: On-line Digital Computer for Measurement of a Neurological Control System. CACM, 5:567-568, 1962.
17. Stark, L., Vossius, G., and Young, L.: Predictive Eye Movement Control. IRE Trans. on Hum. Factors Electronics. HFE-3:52-57, 1962.
18. Telford, C. O.: The Refractory Phase of Voluntary and Associative Responses. Exper. Psych., 14:1, 1931.
19. Tustin, A.: The Nature of the Operator's Response in Manual Control and Its Implications for Controller Design. J. Inst. Electronic Engineers., 94-190, 1947.
20. Ward, J. R.: The Dynamics of a Human Operator in a Control System. Doctoral Dissertation, Dept. of Aeronautics, University of Sydney, 1958.
21. Young, L., and Stark, L.: A Discrete Model for Eye Tracking Movements. IEEE Trans. on Military Electronics, MIL-7, 2-3: 113-115, 1963.
22. Young, L. and Stark, L.: Variable Feedback Experiments Testing a Sampled Data Model for Eye Tracking Movements. IEEE Trans. of the Prof. Technical Group on Hum. Factors in Electronics. Special Manual Control Issue, HFE-4, 1:38-51, September 1963. □

THE EDITOR'S PAGE

BIOENGINEERING—1967

Engineering as science has a rather short history. Up until the second quarter of the present century, engineers looked to chemists and physicists for the basic scientific information upon which they could base their engineering applications—bridge construction, prime movers, power machinery. With the inventions of the telephone, the triode, feedback amplifiers, radio systems, and automatic pilots the development of control and communication engineering systems proceeded. When engineers again turned to physicists and chemists for basic scientific information concerning these complexly organized systems, they found none available: when they turned to biology, they found that biology had not yet developed into an advanced quantitative science. Being intelligent, well-trained and practical men, they developed the science of engineering systems themselves. People like Vannevar Bush, Norbert Wiener, Claude Shannon, Warren McCulloch, John von Neuman, Julian Bigelow, and Hendrick Bode pushed ahead and created what we now know as modern electrical engineering and computer science.

These pioneering individuals were interested in biology as an example of a complexly organized set of systems; and *cybernetics* was well named by Norbert Wiener as "control and communication in animals and machines." Their influence on biology, starting with those engineering scientists who were originally biologists, has grown considerably. A landmark is a special issue of the Proceedings of the Institute of Radio Engineers published in November, 1959 with papers on the frog's eye and on the pupillary servomechanism which give some early examples of careful application of cybernetics to neurophysiology and neurological organization. Three papers in this month's issue of the Presbyterian-St. Luke's Bulletin represent this intellectual impact of engineering science on neurology.

As a young neurologist, trying to make sense of disorders of motor coordination so often seen in a variety of neurological syndromes, I found classical neurophysiology without adequate explanations to offer, and turned to engineering science or cybernetics. Our approach was to define, measure, quantify, analyze, and form concepts of these neurological systems that have the same hard mathematical structure found in the physical sciences. These quantitative descriptions do *not* merely summarize the verbal and intuitive qualitative feelings that neurologists have already well understood. Science proceeds by alternate steps: formulation of an intuitive concept for a new phenomenon, incorporation of the new and other related phenomena into a mathematical structure, and finally again, development of intuitive concepts of further phenomena utilizing the added perspective obtained with the

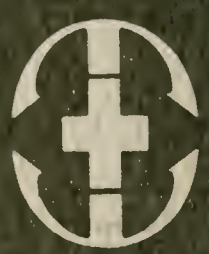
formal elegance of the mathematical model or theory. As an example, we offer the comparison between the first scientific appreciation of gravity as both the force causing the apple to hit Newton's head and the forces acting between planetary bodies, as contrasted with the mathematical formulation of gravitational laws that permit detailed calculations and predictions to be made which are the basis of the current technological ability to make a soft landing on the moon.

Our work has dealt mainly with the engineering science approach to four neurological motor feedback systems:—the pupil, the lens, eyeball rotation, and hand movement, as exemplified by the papers published in this issue. Other ancillary areas include study of the underlying neurophysiological mechanisms, the elements from which these neurological servomechanisms are constructed. These with their neuronal organizations and functions must be analyzed in detail, and here, classical neurophysiological techniques of microelectrode recording and stereotaxic stimulation are combined with the engineering approach to specify information rates, nerve codes, nonlinear operations, and discontinuous transformations of signal flow. Finally, our approach also utilizes digital and analog computers to make mathematical models of these neurological systems so that explicit quantitative formulations can be integrated and understood.

While this intellectual research is exciting and compelling for those of us engaged in it, we realize that bioengineering like engineering itself also has a more practical and service-oriented side. The Biomedical Engineering Department of the Presbyterian-St. Luke's Hospital has two sections entirely devoted toward cooperative studies and assistance to the operating departments and the individual medical researchers in the hospital. The Medical Engineering Section under Dr. Robert Arzbaecher is available for engineering consultation, advice and help in the area of biomedical instrumentation and on-line computer data processing. The Hospital Computing Section under Dr. Jerald Brodkey, besides operating the hospital digital computer in our department on 9-Jelke-South Center, cooperates with the Medical Engineering Section for on-line computer projects, and also has sole responsibility for off-line computer data processing, the more usual type of scientific use for digital computers. We hope that our interactions with the rest of the hospital will be fruitful both in the intellectual research arena and in the cooperative introduction of bioengineering techniques for patient care.

Lawrence Stark, M.D., Chairman
Department of Biomedical Engineering
Special Editor

PRESBYTERIAN-ST. LUKE'S HOSPITAL MEDICAL BULLETIN



PRESBYTERIAN-ST. LUKE'S HOSPITAL

MEDICAL BULLETIN

VOL. 6 NO. 3 JULY 1967

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Abstracts and Reviews

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97. **Abstracts and Reviews**

MODIFICATION OF AORTIC PRESSURE PULSE BY LEFT BUNDLE BRANCH BLOCK IN AORTIC STENOSIS*

Djavad T. Arani, M.D.[1]
Richard A. Carleton, M.D.[2]

INTRODUCTION

In the course of studies of patients with aortic stenosis, three patients were encountered who had left bundle branch block and an unexpectedly low first derivative of the central aortic pressure.[1] A reduced rate of ventricular or arterial pressure rise has been shown with abnormal, asynchronous electrical excitation of ventricular muscle in experimental animals.[2]

The present report concerns hemodynamic studies in a patient with aortic stenosis in whom left bundle branch block could be produced at will.

CASE REPORT

W. S. was a 64 year old man who had experienced slowly worsening angina pectoris for 8 years. A murmur had first been noted 6 years ago. He had never experienced chest pain exceeding 5 minutes in duration or dyspnea.

On examination, his blood pressure was 124/70 mm Hg and his pulse was 76 beats per minute. Only the cardiovascular examination was abnormal. A forceful apical impulse was palpable in the 6th intercostal space 2 cm left of the midclavicular line. The aortic closure sound was decreased in intensity. A Grade V systolic ejection murmur was maximal in the 2nd interspace and radiated to the carotid vessels. A Grade I brief diminuendo diastolic murmur was heard at Erb's point.

The electrocardiogram was normal. Chest roentgenograms showed left ventricular enlargement, slight dilatation of the ascending aorta, and calcification of the aortic valve.

Cardiac catheterization was carried out using an 8 French catheter, with two channels terminating at the tip and 10 cm back from the tip, placed in the

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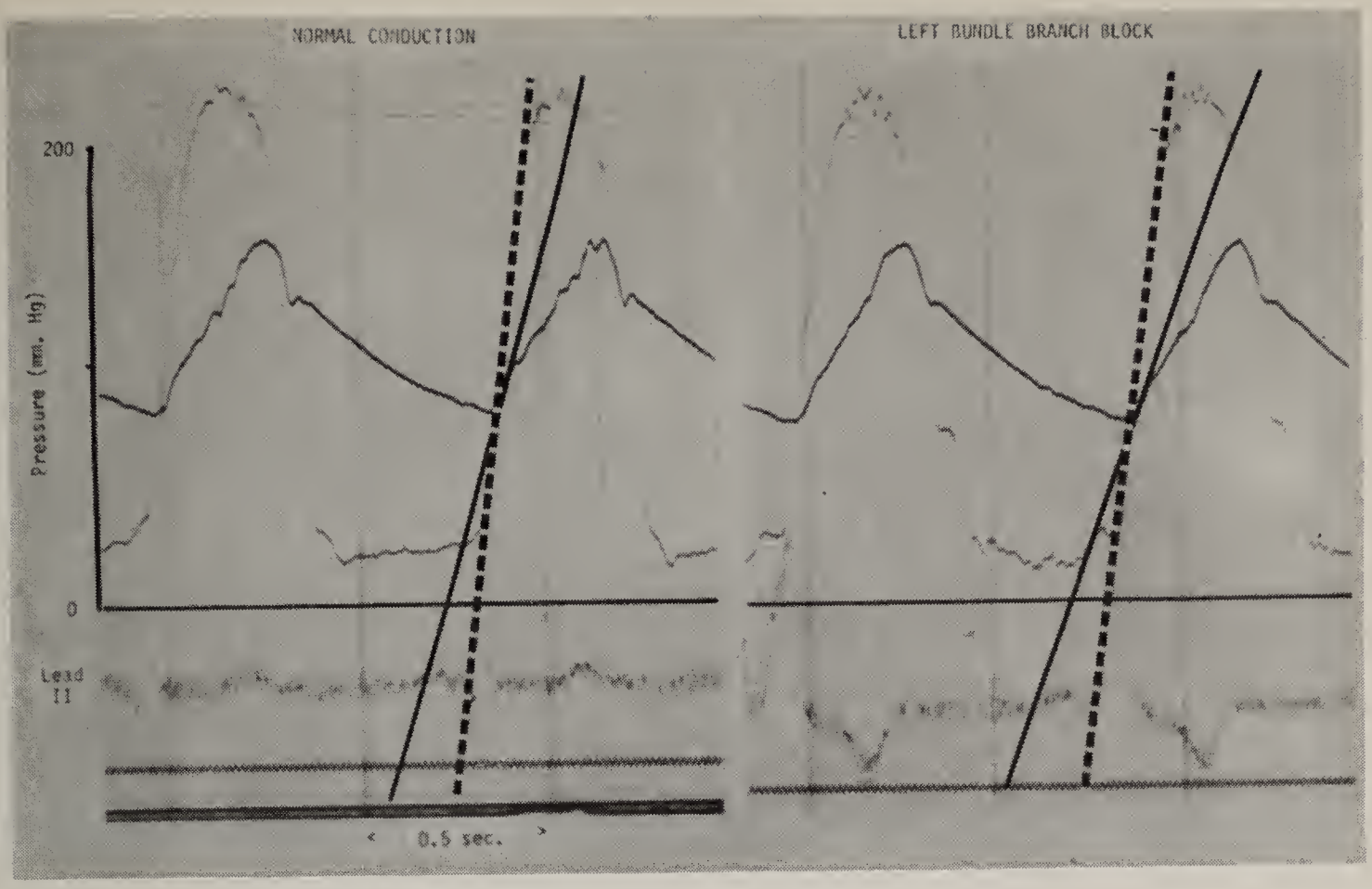

Fig. 1.—Electrocardiogram left ventricular and aortic pressure tracings during normal conduction (left panel) and left bundle branch block (right panel). The solid lines and darkened lines indicate the slope of the rising aortic and left ventricular pressure respectively.

left ventricle and aorta 5 cm above the valve respectively. Pressures were recorded with equisensitive strain gages and an optical galvanometer-photographic paper system. The frequency response of this system is 18-20 cycles per second. Pressures were measured directly. The first derivatives of left ventricular and aortic pressures were measured by determining the slope of the rising pressure curve. The segment of aortic pressure used was the 0.06 secs preceding the anacrotic notch.

Advancing and withdrawing the catheter 0.5 cm. along the left ventricular septum was associated with a reproducible abrupt change in electrocardiographic leads I, II, and III, from normal to left bundle branch block QRS complexes without changes in sinus nodal rate or in P-R interval. Differences between measurements of 20 beats with and without left bundle branch block have been subjected to Student's t test.

Representative pressure tracings are shown in Figure 1. Severe aortic stenosis was found, with a calculated valvular area of 0.9 cm.^{2} The duration of the QRS complex changed from 0.08 secs to 0.13 secs with the appearance of left bundle branch block; concomitant secondary T wave changes occurred. The left ventricular end-diastolic and peak systolic pressures and aortic systolic and diastolic pressures were not different. The time between the onset of the QRS complex and onset of aortic pressure rise was 0.03 secs longer with left bundle branch block than with normal conduction.

The rate of rise in left ventricular pressure was 1345 (S.E. $= 6$) mm Hg per sec with normal conduction and fell significantly to 1073 (S.E. $= 16$) mm Hg per sec with the induction of left bundle branch block. The corresponding values in the aortic pressure were also significantly different: 443 (S.E. $= 7$) mm Hg per sec without and 340 (S.E. $=$ 4) mm Hg per sec with left bundle branch block ($p < 0.01$). The rate of fall in ventricular pressure was, however, not different.

COMMENT

The studies of Klotz and his associates have shown the influence of the site of initial ventricular excitation on the mechanical performance of the heart.[3] Gilmore, *et al*[2] have studied the influence of normal and of abnormal ventricular excitation. They have shown reduced myocardial function whether expressed as ventricular function curves or as the rate of ventricular pressure generation.

The ventricular activation sequence is abnormal in left bundle branch block[4] and reduces the synchronicity of ventricular fiber contraction. The associated lessened mechanical effectiveness produced the changes seen with left bundle branch block in this patient.

The arterial pulse contour has been analyzed in an effort to assess the presence and severity of aortic stenosis.[4,5] The present data indicates that left bundle branch block significantly alters the arterial pulse contour in aortic stenosis. This modification in pressure must be considered in efforts to evaluate aortic stenosis from arterial pressure curves.

SUMMARY

Hemodynamic data from a man with severe aortic stenosis and reproducible left bundle branch block are presented. Left bundle branch block significantly altered the left ventricular and aortic pressure pulse. □

REFERENCES

1. Arani, D. T., Carleton, R. A., and Graettinger, J. S.: Diagnostic Value of the Aortic Pressure Pulse in Aortic Stenosis. (Manuscript in preparation.)
2. Gilmore, J. P., Sarnoff, S. J., Mitchell, J. H., and Linden, R. J.: Synchronicity of Ventricular Contraction: Observations Comparing Haemodynamic Effects of Atrial and Ventricular Pacing. Brit. Heart J., 25:299, 1963.
3. Klotz, D. H., Lister, J. W., Jomain, S. L., Hoffman, B. F., and Stuckey, J. H.: Implantation Sites of Pacemakers after Right Ventriculotomy and Complete Heart Block. J.A.M.A., 186:143, 1963.
4. Seidenstein, M. H., Hoffman, B. F., Stuckey J. H., Venerose, R. S., and Michaels, L.: Activation of Epicardial Surface of Left Ventricle Following Left Ventriculotomy and Left Bundle-branch Block. Amer. J. Cardiol., 10:101, 1962.
5. Hancock, E. W., and Abelmann, W. H.: A Clinical Study of the Brachial Arterial Pulse Form with Special Reference to the Diagnosis of Aortic Valvular Disease. Circulation, 16:572, 1957.
6. Delman, A. J., Gordon, G. M., Eisenberg, R., Escher, D. J. W., and Rosenblum, R.: The Direct Brachial Arterial Pulse-pressure curve in the Evaluation of Patients with Aortic Valvular Stenosis. Amer. Heart J., 69:582, 1965. □

BLOOD LEVELS, TOXIC AND ANTI-NEOPLASTIC EFFECTS OF L-ASPARAGINASE PREPARATIONS FROM E. COLI AND GUINEA PIG SERUM*

William C. Dolowy, M.S., D.V.M.[1]
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INTRODUCTION

A protein fraction isolated from Escherichia coli (E. coli) cells has been shown to cause regression of the subcutaneous and intracranial 6C3HED mouse lymphoma.[1,2] This preparation possesses L-asparaginase (L-Ase) activity. L-asparaginase activity has been correlated with the antitumor activity of protein fractions isolated from other sources such as guinea pig serum.[3,4,5]

Recently, it was shown that an L-asparaginase prepared from yeast[6] does not exert antitumor activity in mice. This was correlated with and attributed to its rapid disappearance from the blood, whereas guinea pig serum L-asparaginase was detectable for 3 days. In the present study, we investigated the blood levels in normal mice of L-asparaginase after administration of partially purified enzyme from guinea pig serum and 4 partially purified preparations of L-asparaginase from E. coli, as well as the effectiveness of 2 of the E. coli preparations against the subcutaneously implanted 6C3HED mouse lymphoma. Earlier, it was shown that partially purified L-asparaginase from guinea pig serum caused regression of leukemic organ enlargement and lowered lymphoblasts in peripheral blood in a child with acute lymphoblastic leukemia.[5] Since more highly purified L-asparaginase can be obtained from E. coli than from the guinea pig serum, the preparations from E. coli are being investigated for antitumor activity and toxicity.

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TABLE 1. EFFECT OF L-ASPARAGINASE FROM E. COLI ON C3H MICE WITH IMPLANTED 6C3HED LYMPHOSARCOMA.

SOURCE OF ANIMALS	NO. OF ANIMALS	TUMOR CELLS	ROUTE OF TUMOR CELLS	L-ASPARAGINASE				MEAN DAYS TO DEATH	SACRIFICED FOR HISTOPATHOLOGY			SURVIVORS AT DAY AFTER TUMOR CELLS INJECTED			CLINICAL SYMPTOMS AT SACRIFICE
				Origin	Units per gram body wt.	Days after tumor cells	Specific activity		No. of animals	Days after tumor inoculated	Survivors at day of sacrifice	75 da.	116 da.	262 da.	
Experiment 1															
HVA	3	10^8	SC	Worthington	20	7	104	>192	—	—	—	2/3	2/3	2/3	—
HVA	4	10^8	SC	Idem	10	7	104	>148	—	—	—	2/4	2/4	2/4	—
HVA	10	10^8	SC	—	None	—	—	15.1	—	—	—	0/10	0/10	0/10	—
Experiment 2															
HVA	5	10^7	SC	—	None	—	—	14.6	—	—	—	0/5	—	—	—
HVA	10	10^7	SC	U. of Ill.	1.7	8	60	19.8	—	—	—	0/10	—	—	—
HVA	10	10^7	SC	Idem	5	8	60	>29.4	—	—	—	1/10	—	—	None
HVA	10	10^7	SC	Idem	15	8	60	>64.2	—	—	—	7/10	—	—	Idem
HVA	10	10^7	SC	Idem	45	8	60	>68.8	—	—	—	7/10	—	—	Idem
Experiment 3															
CU	5	10^7	SC	Worthington	0	—	—	21.6	—	—	—	0	—	—	—
CU	5	10^7	SC	Idem	1.7	8	346	27.8	—	—	—	0	—	—	—
CU	10	10^7	SC	Idem	5.0	8	346	34.8	—	—	—	0	—	—	—
CU	10	10^7	SC	Idem	15.0	8	346	>116	—	—	—	10	10	—	—
CU	10	10^7	SC	Idem	45.0	8	346	>116	—	—	—	10	10	—	—
CU	10	10^7	SC	Idem	135.0	8	346	>116	—	—	—	10	10	—	—
Experiment 4															
HVA	5	10^7	SC	U. of Ill.	15	8	60	—	5	9	5	—	—	—	Tumors much smaller than of non-treated.
HVA	5	10^7	SC	Idem	15	8	60	—	5	10	5	—	—	—	Idem
HVA	5	10^7	SC	None	—	—	—	—	5	10	5	—	—	—	—

MATERIALS AND METHODS

Tumors and Mice

The solid form of 6C3HED lymphosarcoma was prepared and administered as described previously.[5] C3H mice from Cumberland View Farms weighing 18-25 grams and from Hines Veterans Administration Hospital weighing 25-30 grams were used for each experiment. The cells were inoculated subcutaneously at the posterior margin of the last rib for mean-day-to-death and pathology experiments.

Enzyme

Two of the L-asparaginase preparations used were prepared in our laboratory and were extracted from E. coli or guinea pig serum according to procedures described previously.[1,2,7] A similar preparation of E. coli L-asparaginase was purchased from Worthington Biochemical Corporation and was used in experiment 1. Chromatographically purified E. coli L-asparaginase used in experiment 3 and in pyrogen tests was donated by Worthington Biochemical Corporation. The assay for L-asparaginase was identical to that described earlier.[5] Protein was determined by the method of Lowry et al.[8] One unit of L-asparaginase is defined here as that amount which will catalyze the liberation of 1 μ mole of NH_3 per hour from L-asparagine under the assay conditions.

Two protein fractions from E. coli which contain asparaginase activity have been described by Roberts et al.[9] One has antitumor activity and one does not, however, they are easily separated from each other during fractionation. The two enzymes can be distinguished by their pH profiles and on this basis it could be shown that the asparaginase preparation obtained from Worthington was predominantly the species with antitumor activity since its activity at pH 8.6 was identical to that at pH 6.4. This would not be the case if the preparation were a mixture of the two enzymes described by Roberts et al.[9]

Blood Levels of L-asparaginase

Blood was collected in heparinized syringes from the hearts of etherized mice at various intervals after intraperitoneal injection of L-Ase. After centrifugation, the plasmas of 5 mice from each dose level were individually assayed for L-Ase activity.

Pyrogen Tests

The minimal pyrogenic dose (MPD-3) of 1 crude and 3 chromatographically purified preparations of E. coli asparaginase was determined in rabbits by the method of Watson and Kim[10] (Table 2). The MPD-3 is defined as the minimum dose of drug per kilogram of body weight which will produce a 1.0°C rise in body temperature at the end of 3 hours. The L-Ase was inoculated intravenously in normal saline (5 mg L-Ase/cc) after sterilization through a 220 mμ Millipore filter. Rectal temperatures were taken immediately prior to and at hourly intervals after inoculation. Twenty or more rabbits were used for each determination, using 5 rabbits for each of 4 doses. Rabbits were never reused for pyrogenicity experiments.

The MPD-3 was also determined for a partially purified guinea pig serum asparaginase; the preparation was described previously.[5] (Table 2)

RESULTS

Tumor Bearing Mice

In all mice used in all experiments, tumor diameters were approximately 1 cm in diameter at 7-8 days after cells were injected (Table 1). The tumors of animals treated with 15 units of L-asparaginase per gram of body weight became much smaller within 24 hours after treatment, while tumors of nontreated animals enlarged. Histologic appearance

TABLE 2. SPECIFIC ACTIVITY AND MINIMUM PYROGENIC DOSE AT 3 HOURS (MPD-3) OF L-ASPARAGINASE PREPARATIONS, DETERMINED IN RABBITS.

MATERIAL	NO. OF RABBITS USED	SPEICFIC ACTIVITY U/mg WHOLE MATERIAL	MPD-3	U/MPD-3
Guinea pig serum				
L-asparaginase Fl	20	4.0	110 mg/kg	440
E. coli L-asparaginase				
crude	20	91	0.04 mg/kg	3.6
DEAE 6609	20	346	1.5 mg/kg	519
DEAE ASPC 6 GA II	20	535	1.1 mg/kg	588
DEAE ASPC 6 GA I	60	896	1.48 mg/kg	1,323

of the treated regressing tumor cells at 24 and 48 hours was identical to that seen with guinea pig serum L-Ase previously,[3,5] and E. coli L-Ase previously.[2] Pyknosis and karyorrhexis of cells were the primary bases for identifying necrotic cells. There was no calcification of the tela choroidea, as reported previously in mice which recovered from intracranial tumors.[2] Other organs of L-Ase treated animals which were examined and found to be normal included the brain, heart, lung, stomach, intestines, pancreas, liver and kidney.

The tumor bearing mice which were treated with bacterial L-Ase had a longer mean-day-to-death in each of 4 experiments. At doses of 15 units per gram (U/g) or higher the mean-day-to-death was over 530% that of controls in experiment 3, over 400% in experiment 2, and over 1,280% in experiment 1, with a high proportion of the animals still alive and well after 116 days in experiment 3 (Table 1).

The E. Coli L-Ase with a specific activity of 60 produced in our laboratory had an ED(effective dose)$_{50}$ of 11.0 U/g and an estimated ED_{90} of 30 U/g at 44 days. The E. coli L-Ase with a specific activity of 346 supplied by Worthington Biochemical Corporation had an estimated ED_{50} of 8.7 U/g and an estimated ED_{90} of 11.9 U/g at 44 days. The LD_{10} of the latter preparation was greater than 135 U/g.

L-Ase Blood Levels in Normal Mice

The levels of L-Ase in the plasma of normal mice were measured prior to and at various intervals up to 4 days after the intraperitoneal inoculation of L-Ase. L-Ase from partially purified guinea pig serum (PPGPS) with a specific activity of 3.1 persisted in the plasma longer than similar doses of L-Ase from E. coli with specific activities of 104 and 346, respectively (Fig. 1). L-Ase from chromatographically purified E. coli with a specific activity of 346 given at 15 U/g resulted in significantly lower blood level than PPGPS at 4 and 24 hours. When the E. coli L-Ase was given at a high dose, 45 U/g, this resulted in higher plasma levels at 4 hours, but lower levels at 24 hours than the PPGPS at 16 U/g (Fig. 1).

The levels of E. coli L-Ase (S.A. 346) in the plasma of 3 normal female rhesus monkeys were measured prior to and up to 72 hours after intravenous inoculation of E. coli L-Ase with a specific activity of 346, at a dosage of 15,000 units per kilogram of body weight. The blood levels obtained were higher at all times than with either PPGPS or E. coli L-Ase given to mice intraperitoneally (Fig. 2). No adverse clinical signs were elicited; a transient twofold rise in BUN on the 1st to 3rd days, falling to normal levels by the 9th day, was the only abnormal chemical change observed.

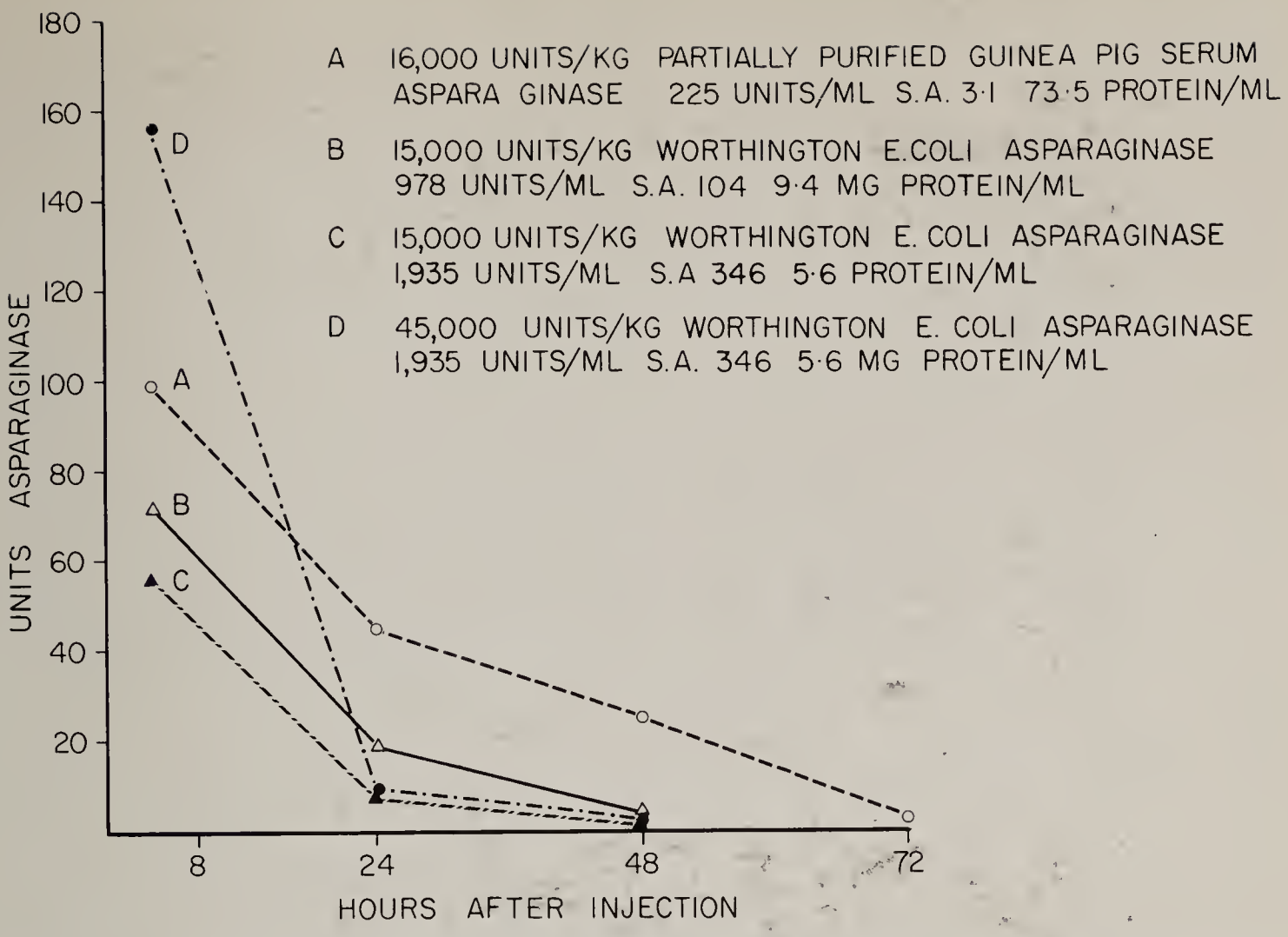

Fig. 1.—L-Asparaginase levels (U/ml) in plasma of mice after intraperitoneal injection of L-asparaginase.

Pyrogenicity in Rabbits

The pyrogenicity of the guinea pig L-Ase was lower than that of E. coli L-Ase per mg of protein. However, the E. coli L-Ase with the highest specific activity also had the least pyrogenicity per unit of asparaginase (Table 2).

DISCUSSION AND CONCLUSIONS

After administration of E. coli L-Ase to mice, the blood levels of L-Ase were considerably lower at 24 hours than the blood levels attained with guinea pig serum L-Ase. In spite of these lower levels at 24 hours, the antitumor efficacy of the E. coli L-Ase appears to be equal to or better than guinea pig serum L-Ase.[5]

The 3 monkeys which received E. coli L-Ase at the ED_{100} level for mice showed no toxic symptoms. A transient rise in BUN was not accompanied by any signs of toxicity.

The mean-day-to-death of mice which were treated with L-asparaginase was related to the dose of the enzyme, and at doses over 15 units/gram body weight the life span of the treated animals was extended over fourfold in one experiment and over twelvefold in another experiment.

The histopathologic appearance of the tumor regressing after treatment with E. coli L-Ase was very similar to that reported for guinea pig L-Ase; it regressed very rapidly and was characterized by extensive necrosis of the tumor.

The pyrogenicity of the L-Ase preparations was ascertained in rabbits.

Although it was possible to obtain E. coli L-Ase with a specific activity of 346-535, in contrast with guinea pig

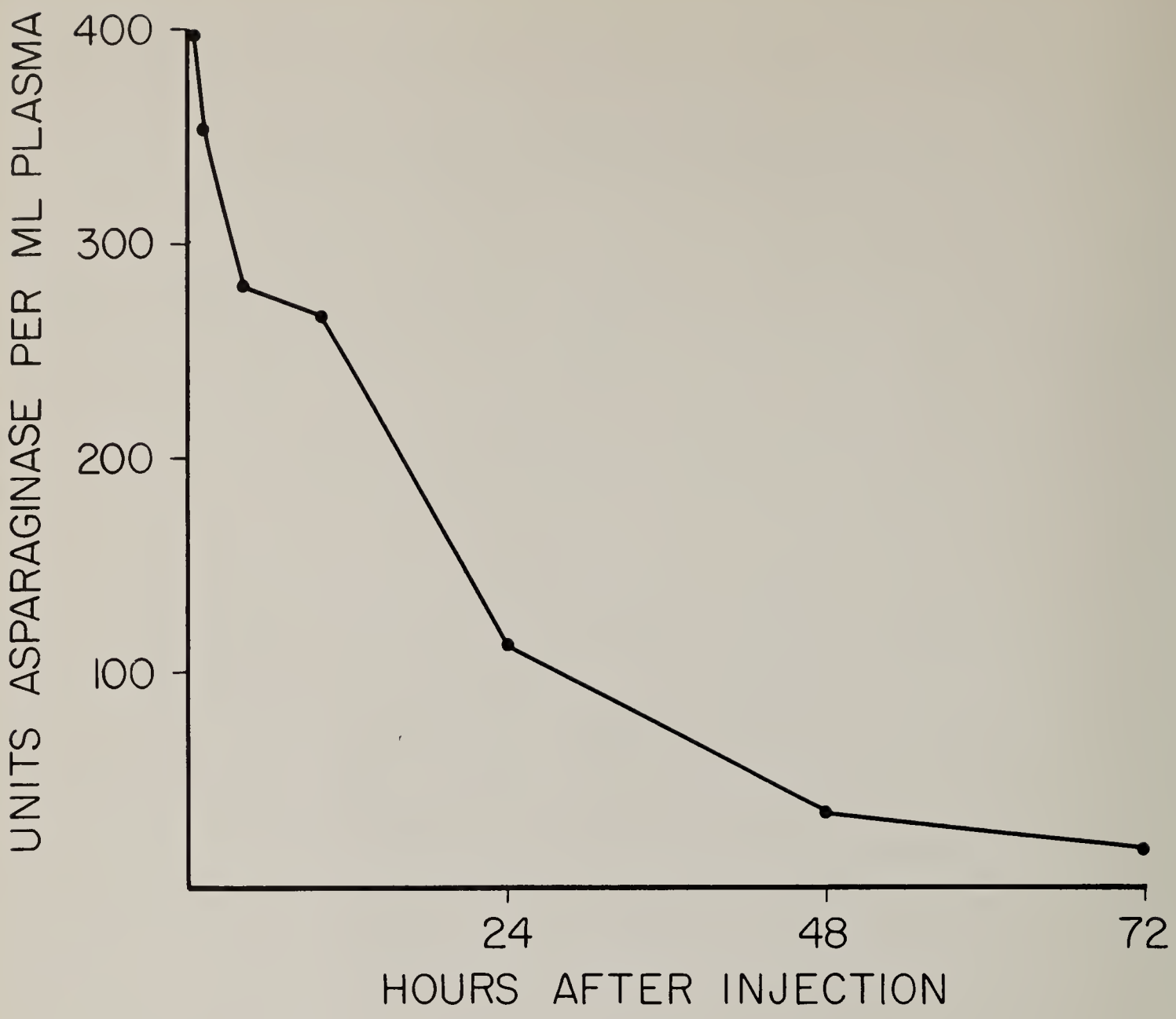

Fig. 2.—Mean plasma levels of L-asparaginase in 3 monkeys after intravenous injection of 15,000 units of E. coli L-asparaginase S.A. 346.

L-Ase with a specific activity of 4.0, the ratio of specific activity to the minimum pyrogenic dose in rabbits at 3 hours was not much better until the E. coli L-Ase was obtained with a very high specific activity, 896. At this activity the U/MPD-3 was 1,323, in contrast with the U/MPD-3 of 440 for guinea pig serum L-Ase.

SUMMARY

After intraperitoneal injection, the rate of disappearance of E. coli L-asparaginase from the plasma of mice was faster than that of a guinea pig serum L-Ase preparation studied previously.

In normal tissues no significant histopathological effects resulted from treatment of mice. The histopathology of regressing tumors was identical to that seen after treatment with guinea pig serum L-Ase.

An E. coli L-Ase preparation with a high specific activity was less pyrogenic than a preparation of guinea pig serum L-Ase in rabbits when expressed per unit of L-Ase activity, even though it was more pyrogenic per mg of total protein.

REFERENCES

1. Mashburn, L. T. and Wriston, J. C.: Tumor Inhibitory Effect of L-asparaginase from Escherichia Coli. Arch. Biochem., 105:450, 1964.
2. Dolowy, W. C., Cornet, J., Henson, D. and Ammeraal, R.: Response of Intracerebral Gardner Lymphoma to Guinea Pig L-asparaginase and Escherichia coli L-asparaginase. Proc. Soc. Exp. Biol. Med., 123:133, 1966.
3. Kidd, J. G.: Regression of Transplanted Lymphomas Induced in Vivo by Means of Normal Guinea Pig Serum, I & II. J. Exp. Med., 98:565, 583, 1953.
4. Broome, J. D.: Evidence that the L-asparaginase Activity of Guinea Pig Serum is Responsible for its Antilymphoma Effects. Nature, 191:1114, 1961.
5. Dolowy, W. C., Henson, D., Cornet, J. and Sellin, H.: Toxic and Antineoplastic Effects of L-asparaginase. Study of Mice with Lymphoma and Normal Monkeys and Report on a Child with Leukemia. Cancer, 19:1813, 1966.
6. Broome, J. D.: Antilymphoma Activity of L-asparaginase in Vivo: Clearance Rates of Enzyme Preparations from Guinea Pig Serum and Yeast in Relation to their Effect on Tumor Growth. J. Nat. Cancer Inst., 35:967, 1965.
7. Meister, A., Levintow, L., Greenfield, R. E. and Abendschein, P. A.: Hydrolysis and Transfer Reactions Catalyzed by Co-Amidase Preparations. J. Biol. Chem., 265:441, 1955.
8. Lowry, O. H., Rosebrough, N. J., Farr, L. A. and Randall, R. J.: Protein Measurement with the Folin Phenol Reagent. J. Biol. Chem., 193:265, 1951.
9. Roberts, J., Prager, M. D. and Bachynsky, N.: The Antitumor Activity of Escherichia Coli L-asparaginase. Cancer Res., 26:2213, 1966.
10. Watson, D. W. and Kim, Y. B.: Bacterial Endotoxins. M. Landy and W. Braun (eds.): Rutgers University Press, New Brunswick, New Jersey, p. 522, 1964. □

ELECTROPHORETIC SEPARATION OF LACTIC DEHYDROGENASE (LDH) ISOENZYMES ON CELLOGEL STRIPS*

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INTRODUCTION

The lactic dehydrogenases (LDH) of human and animal tissues have been separated by zone electrophoresis into at least five molecular forms called isoenzymes[1]. The term isoenzyme denotes enzymatically active proteins, catalyzing the same reaction in the same species, but differing in various of their physicochemical and kinetic properties. LDH isoenzymes are distinguished by numbering them according to their electrophoretic mobilities in the pH range of 7 to 9. In the convention employed here, the number 1 is assigned to the isoenzyme with greatest anodic mobility (negative charge) and the number 5 is assigned to the isoenzyme with the least mobility. Isoenzymes with intermediate and decreasing order of anodic mobilities are assigned the numbers 2, 3, and 4.

Each tissue has a characteristic but not unique distribution pattern of LDH isoenzymes. For example, heart, kidney, and erythrocytes contain predominantly LDH_1 and LDH_2, whereas liver and skeletal muscle contain higher amounts of the slower migrating isoenzymes, LDH_4 and LDH_5. Other tissues such as lung, adrenal, thyroid, spleen, and pancreas contain higher proportions of the isoenzymes with intermediate mobilities.

The normal LDH isoenzyme pattern of a body fluid may be altered to reflect the pattern of a diseased organ in various pathologic processes which involve tissue damage. Examples are myocardial infarction and infectious hepatitis. In the former case, there is a relative increase in serum of LDH_1, and LDH_2, the characteristic isoenzymes of heart tissue. In the latter case, there is a relative increase in serum of LDH_4 and LDH_5, the predominant isoenzymes of liver. Such characteristic changes in serum isoenzyme distribution may be seen even though the total serum LDH activity is within "normal" limits. Thus, the accuracy and reliability of serum LDH determinations as a diagnostic test may be significantly increased in certain instances by the separation of LDH into its isoenzymes.

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The method of electrophoretic separation described here is simple, sensitive, yields consistent results, and employs equipment usually available in most clinical laboratories.

I. Equipment and Reagents

A. *Cellogel electrophoresis strips.* (Colab Laboratories, Inc., Chicago Heights, Ill., U.S.A.) Strips 2.5 x 12 cm are normally used.

B. *Cellulose acetate strips.* (Colab Laboratories) Strips 2.5 x 12 cm are used as incubation strips.

C. *Electrophoresis Apparatus.* Colab Universal Electrophoresis Apparatus and Vokam Constant Voltage/Constant Current D.C. Power Supply were used. However, any horizontal electrophoresis tank may be employed as well as any power supply that provides a well-regulated, filtered output.

D. *Electrophoresis Buffer.*
7.84 g anhydrous sodium acetate
20.00 g sodium diethylbarbituric acid
6.84 ml 2 N HCl
4 liters of distilled water
pH 8.60

E. *Staining Solution.* Prepare immediately before use. The quantity given is sufficient for staining eight strips, 5 x 12 cm.

1. Place 0.45 ml of 60% sodium lactate (53% *L*-lactate content) in a test tube.
2. Add 3 ml of electrophoresis buffer.
3. Dissolve 14 mg of nicotinamide adenine dinucleotide (NAD) in 2 ml of electrophoresis buffer and add to above solution.
4. Dissolve 16 mg nitro blue tetrazolium (NBT) in 2 ml of electrophoresis buffer and add to above solution.
5. Dissolve 1.2 mg of phenazine methosulfate (PMS) in 1 ml of electrophoresis buffer and add to above solution.

The solubility of the NBT salt varies with producer and lot. Care must be taken to dissolve it completely in buffer before adding the PMS, as undissolved particles give uneven staining and cause blue spots to appear in the cleared strip. The sodium lactate-NAD-NBT mixture and the PMS solution can be stored separately in the dark at 4°C for several hours. The complete staining solution is less stable and is sensitive to exposure to light.

F. *Fixing Solution.*
5 ml glacial acetic acid
5 ml ethanol (95%)
90 ml distilled water

G. *Decolorizing Solution.*
500 ml 5% acetic acid
450 ml ethanol (95%)
50 ml 4-hydroxy-4-methyl-2-pentanone

H. *Cellogel Solvent.* Acetone

II. Preparation of the Sample and Standard

A. *Collection.* Obtain unhemolized serum from fresh venous blood. It may be refrigerated until used but do *not* freeze. Hemolyzed blood or blood obtained by finger-prick cannot be used as erythrocytes and skin cells contain high levels of LDH.

B. *Concentration.* A serum LDH activity of 1000 units per ml is required for the detection of all five isoenzyme bands. The optimum operating range is 1200-1600 units per ml (1 unit = decrease in absorbance in a 1 cm light path at 340 mμ of 0.001 per min. per ml at 30°C). Sera with lower activity should be concentrated. Sera can be readily concentrated by positive pressure filtration with a MD class high pressure apparatus (Schleicher and Schuell Company, Keene, New Hampshire, U.S.A.) using N_2 gas. MD50 and MD70 filters are used routinely with LSG-60 membranes and have a maximum pressure capacity of 15 atmospheres. LSG-60 membranes have an average pore diameter of 5 millimicrons and exclude proteins with molecular weights above 10,000. About ½ hr. is required to concentrate 3 ml of serum to 0.5 ml.

Dialysis against polyethylene glycol may be used to concentrate serum samples, but this requires more time

and gives more diffuse isoenzyme bands upon subsequent electrophoresis.

Sample volumes of 2-5 microliters, containing 2 to 3 units of activity, are usually applied. Larger volumes may be used but the separated isoenzyme bands are broader.

A serum standard is prepared by concentrating normal serum 4 to 6-fold; i.e., to approximately 1500 units per ml. Bromphenol blue (5 to 6 granules) is added to 5 ml of concentrated serum to tag the albumin and serve as a visual marker during electrophoresis.

III. Electrophoresis Procedure

A. *Preparation of tank and strips*

1. Pour about 700 ml of electrophoresis buffer into the tank; tilt the tank forward to insure that the solution is level in all compartments.
2. Soak 2.5 x 12 cm Cellogel strips in electrophoresis buffer for 15 minutes.
3. Remove strips from the buffer solution and blot gently with filter paper.
4. Position strips in the tank with the opaque side upward; i.e., glossy side down. Connect strips to the buffer system through filter paper wicks. A bridge gap of approximately 8 cm is used.
5. Apply a current of 0.5-0.75 milliamperes per 2.5 cm strip (150-200 volts) and allow to run for 3-5 minutes to effect equilibrium. Turn off current before applying samples.

B. *Sample Application*

Apply samples with glass capillary tubes (0.5-0.9 mm I.D.) or graduated lambda pipettes with pointed tips. Apply a volume of 2-5 microliters, containing 2-3 units of activity, to the opaque side of the strip at a point 1/3 of the bridge gap from the cathode end. The applicator may be guided back and forth along the edge of a ruler placed on top of the tank. Apply samples in a narrow line at the origin, leaving a margin at either edge of the strip. Two or three samples may be placed on a 2.5 x 12 cm cellogel strip. Include a standard serum with each electrophoresis run.

C. *Electrophoresis*

Apply a constant current of 0.5-0.75 milliamperes per 2.5 cm strip for 1½ hours. The starting voltage should be 150-200 volts. The standard serum serves as a marker, with the blue albumin migrating ahead of the fastest LDH band.

D. *Development of the strips*

1. Turn off the current and remove the electrophoresis strips. Prepare incubation strips of cellulose acetate by first floating them on top of the staining solution, then immersing completely. Remove each strip from the stain, allowing excess liquid to drop off. Place the incubation strips on a clean glass plate and lay the enzyme strips (electrophoresis strip) *opaque side down* on the incubation strips, making certain no air bubbles are trapped beneath the strips. Place the glass plate containing the strips in a moist, air-tight plastic container and incubate in the dark at 37°C to develop the isoenzyme bands.
2. Optimum developing time is 1-2 hours; samples of very high activity reach maximum staining in 5-10 minutes. If a longer time is required, place moistened filter paper in the chamber with the plate and continue development up to 20 hours. One and ½ hrs. is suggested for routine serum analysis.
3. Remove strips from the plate and fix by immersing for 3-5 minutes in Fixing Solution. Transfer strips to a distilled water bath. The strips may be stored in distilled water without fading if they are not exposed to ultraviolet light.

E. *Quantitation*

Strips may be examined by visual reading, colorimetric evaluation, densitometric scanning, or elution and

spectrophotometric assay. Colorimetric evaluation is the most satisfactory method and does not require expensive scanning equipment.

1. *Visual examination*
   Visual examination is done while strips are in the distilled water bath, as the color fades slightly when strips are dried.
2. *Colorimetric Evaluation*

a. Remove strips from the distilled water bath, blot with filter paper, and cut each of the stained bands. Prepare a blank using an unstained portion of the strip.

b. Place each section in a test tube and add 4 ml acetone to dissolve the section. Let stand 5 minutes, then shake well.

c. Determine the Optical Density of each fraction with a spectrophotometer or colorimeter at 353 mμ setting the O.D. at zero with the prepared blank. The % of each LDH fraction present in the serum is the % O.D. for that fraction divided by the total O.D. for all bands. Should it be desired to clear the Cellogel strips for preservation the following technique will suffice:

Remove the strips from the distilled water bath and place in Decolorizing Solution for 10 minutes. Remove each strip and place on a clean glass plate, opaque side down, making certain no air bubbles are trapped underneath the strip. Do not blot. Immediately place in an oven preheated to 60-75°C until the strips are transparent, about 5-10 minutes. Allow the plate to cool and gently peel strips away from the glass, starting from one corner. If strips adhere to the plate, remove by flooding the plate with hot water.

DISCUSSION

Examples of the electrophoretic separations obtained are shown in Fig. 1. These strips were somewhat overloaded with enzyme activity in an attempt to provide better contrast for photography. Consequently, the separated isoenzyme bands are broader than usually obtained. Nevertheless, the differences in patterns amongst the various samples are evident. The relative increases in LDH_1 and LDH_2 in myocardial infarction (B) and of LDH_5 in infectious hepatitis (C) as compared to normal serum (A) are clearly discernible. It should be noted that the same amount of enzyme activity (4 units) was applied in each case. It is recommended that a normal human serum be included in each electrophoretic series and that comparable amounts of total enzyme activity are used for all samples. This will minimize the possibilities of false negative and false positive interpretations.

Strips D, E, and F show respectively the isoenzyme patterns for homogenates of human heart and liver, and for a lysate of human erythrocytes.

The technique described here has certain advantages over the techniques employing agar-gel[2] or starch gel[3] for routine electrophoresis. The Cellogel strips are available as such and no preparation of gels is necessary. The Cellogel technique is sensitive to less than 0.1 unit of LDH activity, whereas the gel techniques require the application of some 150 to 200 units of enzyme activity to detect five isoenzymes. The subbands present in the erythrocyte (Fig. 1, strip F) are usually not seen in gel electrophoresis. Cellulose acetate strips[4] are also highly suitable for separation of LDH isoenzymes; however, we find the separations on Cellogel to be consistently better than those obtained with cellulose acetate.

With regard to the "quantitation" of the separated isoenzyme bands, we believe that visual inspection by the practiced eye is sufficient to detect abnormal patterns. This is especially so if a standard normal serum is included and comparable enzyme activity employed in each electrophoretic series. Furthermore,

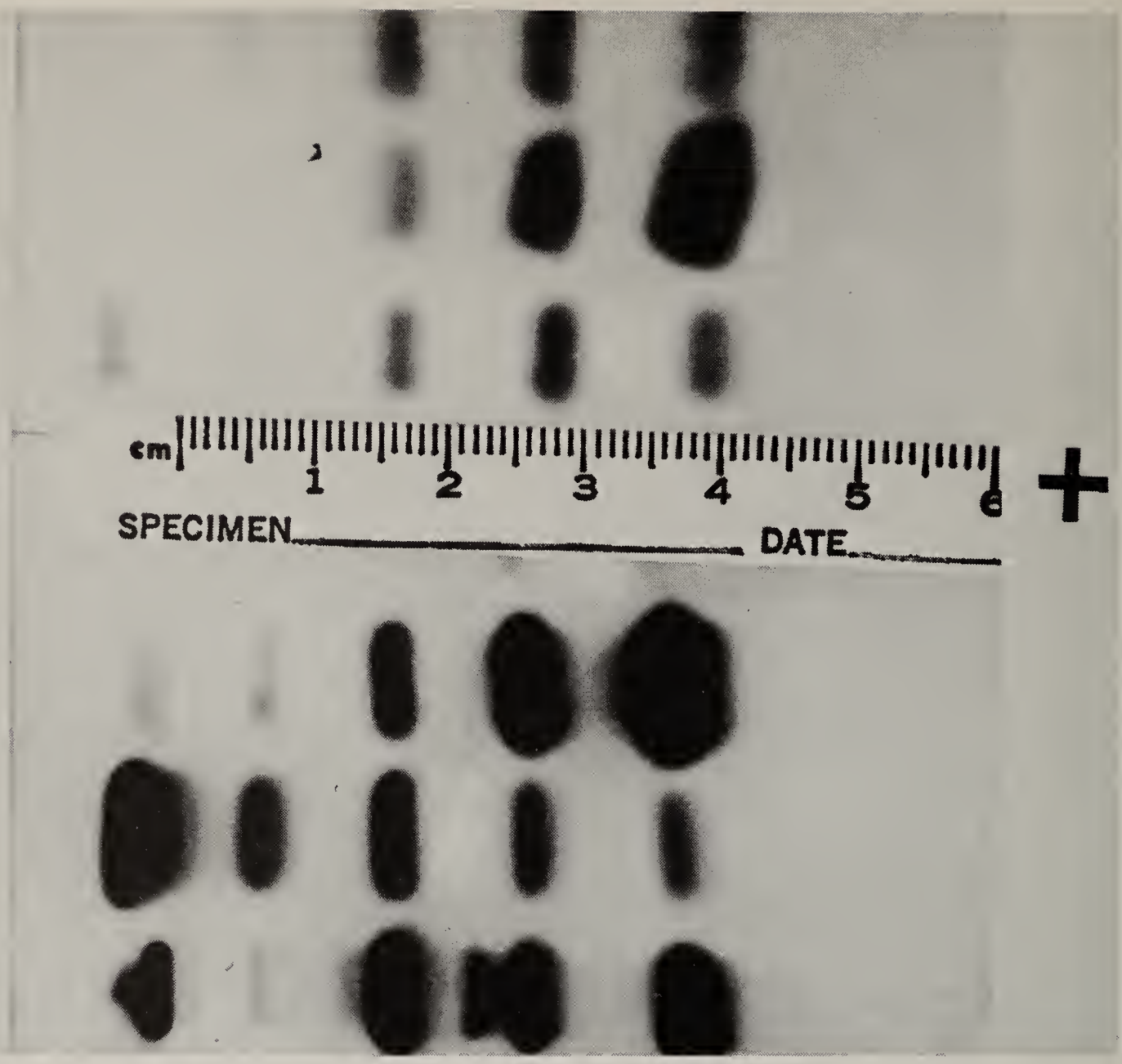

Fig. 1.—Electrophoretic Separation of LDH Isoenzymes of Human Sera and Tissues (A, normal human serum; B, serum from patient 24 hours after myocardial infarction; C, serum from patient with infectious hepatitis; D, homogenate of human heart; E, homogenate of human liver; F, lysate of human erythrocytes. Units of enzyme applied at the zero cm. mark on the scale were 4 for A, B, and C and 5 for D, E, and F).

this technique is only an aid in diagnosis and must be interpreted with other clinical data available to the physician. The assignment of numerical values, for example by colorimetric evaluation, does not enhance the reliability of the technique in view of the fact that each isoenzyme has somewhat different kinetic properties and the conditions are not optimal for each isoenzyme. In addition each analytical technique, be it densitometry, colorimetric evaluation, etc., has its own inherent errors which contribute to the uncertainty of the results. □

REFERENCES

1. Wilkinson, J. H.: Isoenzymes. J. B. Lippincott Company, Philadelphia, 1966.
2. Wieme, R. J., and Van Maercke, Y.: The Fifth (Electrophoretically Slowest) Serum Lactic Dehydrogenase as an Index of Liver Injury. Ann. N. Y. Acad. Sci., 94:898, 1961.
3. Smithies, O.: An Improved Method for Starch-Gel Electrophoresis: Further Variations in the Serum Proteins of Normal Individuals. Biochem. J., 71:585, 1959.
4. Barnett, H.: The Staining of Lactic Dehydrogenase Isoenzymes After Electrophoretic Separation of Cellulose Acetate. J. Clin. Path., 17:567, 1964. □

ABSTRACTS AND REVIEWS

OF PUBLICATIONS BY THE STAFF

Dicken, C. F. and Van Pelt, J. D.: Further Evidence Concerning Acquiescence and the MMPI. *Psychol. Rep., 20:935-941, 1967.*

Ninety-four normal and 100 schizophrenic subjects were tested with the Minnesota Multiphasic Personality Inventory and with a version of the MMPI composed of items reversed in meaning. Comparison of original and reversed items and scales indicated little if any of the variance of the original can be attributed to acquiescence response style. Several item-reversal studies of the MMPI are reviewed and a high degree of consistency is noted.

Garron, D. C. and Cheifetz, D. I.: Stimulus Rotation and Visual Scanning in Subjects with Copying Disability. *Perceptual and Motor Skills, 24:1015-1025, 1967.*

Rotation of squares increases copying difficulty for young children and brain-damaged adults. Explanations stress both perceptual and cognitive factors. Records of visual scanning were used as an index of attention to areas of the stimulus field. Perceptual explanations were translated into scanning terms. The degree to which scanning is consistent with expectations inferred from perceptual theories was examined. Scanning of squares, rotated and unrotated, was compared for 7 normals and 7 adults with impaired copying ability. Variables were attention to contour, enclosed form, and ground. Conclusions were that: (a) normals scan rotated and unrotated squares similarly; (b) impaired subjects scanning of rotated squares is different from normal scanning and from their own scanning of unrotated squares; (c) the differences found do not follow theoretical expectation.

Norton, A. H.: Preliminary Evaluation of a Psychiatric Treatment Service Integrating Children, Adolescents and Adults. *Amer. J. Psychiat., 123:11, 1418-1424, May 1967.*

A still unique therapeutic environment for children and adolescents is to be housed by intent with an adult patient population. The facility being described is a 61 bed psychiatric unit in an 850 bed university affiliated general teaching hospital. In the two year period under evaluation, 158 children and adolescents have comprised ¼ of the total patient population. Ranging in age from six months to 17 years they occupy beds in single, two and three bed rooms on the top two floors of the hospital. Children are mixed with adult patients on both open and closed wards, and the length of stay varied from one week to 22 months, averaging 12 weeks per patient. Though all patients occupy the same area, there is a separate team of nurses, aids, occupational, music, art, drama and recreation therapists who together with psychologists, teachers, resident and attending child psychiatrists compose the Child Psychiatry Inpatient Service.

The design evolved from three basic community needs. First, the medical, surgical and pediatric divisions of the hospital frequently were confronted with acutely or chronically disturbed children and no adequate staff or facility for active management of the problem. Second, there were no other resources in the community where a child could be admitted quickly into a structured treatment program for diagnostic evaluation, acute and long term intensive therapy or combined somatic and psychiatric treatment. Third, there is a woeful lack in most training programs for child psychiatrists in the active management of psychiatric emergencies in children.

From its inception, two fascinating phenomena became apparent. It was observed that when allowed to choose freely, children spontaneously related to and "used" adult patients whose type and level of pathology in some way related to their own, and with whom they could establish effective communication. For example, a seven year old autistic boy made his first tenuous relationship with a young woman who had an acute catatonic reaction.

Initially he sought only physical contact with her at a primitive level that no staff members could have allowed themselves to participate in. Over a period of months this evolved into a verbal relationship which gradually developed toward increasing staff participation. The second observation was of a strong competitive struggle that developed between the children and adult services at all staff levels and having ramifications throughout the total ward structure. This was often expressed in the unit by the complaint of child or adult staff and patient that everything was geared for the other, or the reaction formation that everything should be done to give more to the other group. The understanding and working through of the parallel processes operating in these areas became a vital part of the therapeutic process of all patients and the staff's growth.

Admittedly the evaluation of the unit is from the point of view of the child's therapy; other evaluations from the adults' therapists are forthcoming, but their opinion in general is that the arrangement is favorable and constructive for the adult as well as the child.

Cole, E. R.; Koppel, J. L.; and Olwin, J. H.: Multiple Specificity of Thrombin for Synthetic Substrates. *Nature, 213:405, 1967.*

The enzymatic action of thrombin on a number of synthetic substrates has been studied. The results obtained indicate that the specificity of thrombin is not as restricted as formerly believed. In addition to arginine and lysine esters also those of phenylalanine, tyrosine, tryptophane and histidine were found to be hydrolysed, although at considerably slower rates. Substitution on the alpha-amino group greatly increased substrate susceptibility to hydrolysis by thrombin.

Cross-reactivity of proteolytic enzymes to certain substrates is not unique in enzymology, and it is not surprising that thrombin also has this ability. In fibrinogen thrombin is known to break only arginylglycine bonds; however, in view of the various other physiological phenomena in which it has been shown to participate, it may well exhibit multiple specificities toward a number of other peptide linkages.

Olwin, J. H. and Koppel, J. L.: Little Publicized Aspects of Thromboembolism. *Med. Clin. N. Amer., 51:151, 1967.*

This paper discusses some of the little publicized aspects of thromboembolism including: (1) some of the less well known effects of heparin, (2) the possible influence of stress, (3) clinical conditions characterized by microthrombosis, and (4) the possible relation of (a) plasma lipids, (b) gout, and (c) smoking to the thrombotic tendency.

Bader, K.: Organ Deposition of Silver Following Silver Nitrate Therapy of Burns. *Plast. Reconstr. Surg., 37:550-551, 1966.*

In order to ascertain whether silver had passed into the circulation of two burn patients treated with silver nitrate solution, postmortem organ analysis was performed by the microincineration technique, as well as limited premortem studies in one patient.

The initial patient was a 66 year old male who experienced a 20% burn of third degree depth. The area of burn was successfully treated with 0.5% silver nitrate dressings for 30 days, but the man died of a cerebral malignancy. The second case was a boy of 18 years who was admitted with third-degree burns over 96% of his body. The massive burn was remarkably well managed with silver nitrate dressings, but the patient died of respiratory complications after seven days. Nearly each organ examined in these patients, as well as premortem urine and blood, revelaed major increases in silver levels such as the spleen at 0.23 P.P.M., liver at 0.44 P.P.M. and muscle elevated to 2.0 P.P.M.

Dilute silver nitrate solutions used in burn therapy, even for short periods of time, may result in silver absorption into systemic circulation and in surprisingly sizable end organ deposition. The practical physiologic significance of these silver levels, if any, is open to question.

de Takats, G.: Microcirculation: The Last Frontier. *J. Cardiov. Surg., Special Issue of VII Congress, Internat., Cardiov. Soc., Philadelphia, pp. 13-42, Sept. 16-18, 1965. Edizioni Minerva Medica, Torino.*

There are definite and ever-growing clinical applications of the knowledge of microvascular responses. Microcirculation has been the neglected "third force" in the cardiovascular circuit. In spite of the spectacular advances taking place in cardiac and major vascular surgery, tissue nutrition remains inadequate and cardiovascular repair is futile should microcirculation fail.

After defining the microscopic and ultramicroscopic areas involved, the acute and chronic forms of microcirculatory involvement are discussed. The behavior of microcirculation in various types of shock, during cardiopulmonary by-pass and after local injuries due to mechanical trauma, cold, burn and electricity are described.

In the chronic phase, the microangiopathies due to hypersensitivity, collagen diseases, diabetes, hypertension, gout, microembolism and microthrombosis are enumerated. Of the regional disturbances, cerebral, renal and splanchnic microangiopathy are surveyed. Postischemic, postsympathectomy and postphlebitic microcirculatory changes are presented.

All forms of treatment aim to improve and maintain adequate perfusion pressure through the microvascular bed. Increasing cardiac output, elimination of excessive vasoconstriction, desludging agents, antithrombotic and fibrinolytic drugs in the acute failure, anti-inflammatory, steroid and immunosuppressive drugs in the chronic failure are discussed Proper selection and proper timing of these agents, some of which are powerful and may be contraindicated when ill-timed, are made on the basis of frequently repeated or continuously monitored tests for microcirculatory failure.

Caldwell, R. G. and Gilchrist, R. K.: Hepaticocutaneous Fistula: Case Report with Surgical Technique for Creation of Fistula. *Surgery, 61:3, 370-371, March, 1967.*

The septic, moribund patient with high common duct obstruction presents a difficult clinical problem. This paper presents such a patient in which a sub-hepatic abscess prevented decompression of the biliary system by drainage of the common bile duct. The liver was decompressed by creation of a hepaticocutaneous fistula which traversed the liver paranchyma. When the patient's condition stabilized Roux-en-Y hepatico-jejunostomy was constructed utilizing the stump of the common duct.

Mehl, R. L.: Trends During Ten Years of Dialysis Treatment. *Proc. E.D.T.A., Lyon, France, June 1966.*

During the ten year period, 1956 to 1966, there have been numerous changes in techniques and emphasis in respect to dialysis of acutely ill patients with renal failure.

Decreased morbity and increased survival has followed the development of safer dialysis equipment, the use of permanent arterial-venous fistulae, earlier and more frequent dialysis, and the prevention of the disequilibrium syndrome through a better understanding and control of water balance. More recently the development and increased early use of peritoneal dialysis, especially in hospital areas outside the major kidney centers, has contributed to overall improvement of results.

The conclusions have been drawn from experience gained from over 1600 dialyses carried out in a metropolitan renal failure unit.

Mehl, R. L.: The Use of Hemodialysis to Supplement the Caloric Intake of Traumatically Injured Anuric Patients. *Proc. E.D.T.A., Lyon, France, June 1966.*

Since, for various reasons, it is frequently difficult or impossible to provide severely injured patients with the 6000 or more calories they may require each day, the use of hemodialysis with high concentrations of glucose in the dialysate is worthy of consideration. With concentrations of 1200 to 1600 mgm. percent it is possible to provide up to 3000 calories

in 6 hours and the dialysis may be repeated every 1 to 2 days. This may be used to supplement other methods of feeding. Water replacement is necessary because the osmotic effects of the technique produce dehydration.

Plotting serial arterial blood concentrations of glucose, during hemodialysis, a plateau is reached within 1 hour. After this time it may be concluded that the rate of glucose infusion is equal to the rate of glucose storage or usage.

Africa, D. L.; Rothner, A. D.; Morales, S. O.; and Christian, J. R.: Exchange Transfusion Bacteremia. *Ped. Digest, 9:5, 27, May 1967.*

The use of antibiotics in exchange transfusions has been questioned even in the presence of a positive blood culture.

Eighty-one blood cultures obtained through the umbilical vein were taken from 27 exchange transfusions. These were done at the start, midway, and after the exchange procedures.

Cultures were also taken from the nose, groin, and umbilical stump prior to the exchange transfusions. The frequency of the positive cultures were as follows: umbilical stump (81.5%), nose (70.4%) and groin (59.3%). Of the 81 blood cultures taken, 30 (37%) were positive. Most of the organisms cultured from the blood were the same as those obtained from the other sites previously made.

Bacteremia after an exchange transfusion was a usual occurrence but it did not necessarily lead to septicemia.

The apparent significance of bacteremia was the fact that organisms lodging in the umbilical stump were introduced into the blood circulation during the process of umbilical vein catheterization. Blood cultures obtained through the umbilical vein were therefore worthless by themselves in evaluating the presence of septicemia.

The use of prophylactic antibiotics after an exchange transfusion was not found to be indicated unless there were existing signs and symptoms of sepsis.

Hyde, J. S. and Saed, A. M.: Acute Bronchiolitis and the Asthmatic Child. *J. Asthma Res., 4:137, 1966.*

A study of 100 hospitalized infants was undertaken to determine if allergic background predisposes to the development of bronchiolitis. Also the possibility that infectious bronchiolitis produced and increases the incidence of bronchial asthma was investigated.

Thirty-one had three or more attacks of asthma. Collateral evidence of atopy in the asthma group included allergic rhinitis and/or eczema in 81% and in the non-recurrent bronchiolitis group, 27% had atopy.

The family history of parents and sibs for asthma was found in 50% of the recurrent group and 46.5% of the non-recurrent bronchiolitis group. Atopic predisposition occurred in 78% of the immediate and close relatives of children with acute bronchiolitis.

RS virus was found to be an etiologic agent in bronchiolitis only during the first seven months of life. RS infection was detected serologically in 6 infants of 17 examined during the 1963-1964 epidemic. Positive RS viral cultures were found among 7 infants of 23 cultured during the 1964-1965 epidemic. Positive coliaerogenes bacterial cultures of the nasopharynx were significantly increased.

The clinical features of infection with atopy are not sufficiently distinct to permit differentiation of bronchiolitis caused by infection without atopy. Diagnosis of atopy can be established with or without infection by: 1. collateral findings, past history and family history of atopy, 2. the previous or subsequent findings of episodes of wheezing, tachypnea, and coughing, 3. viral cultures and changing serological titers for viruses as well as other laboratory tests, 4. seasonal epidemics of RS in the northern temperate zone are usually limited to the months of November through April.

The hypotheses that bronchiolitis is a precursor of asthma is not supported. 45% of patients with three or more attacks of cough, tachypnea, wheezing and retractions had attacks prior to the episode of bronchiolitis under study. These findings suggest that bronchiolitis in many patients is a manifestation of atopy. Children who are prone to asthma often respond to their respiratory infections by developing asthma.

Ryan, W. F.; Economou, P. G.; and Schwartz, T. B.: Intravenous Glucose Tolerance Test in an Industrial Population: *Controls, Subjects with Coronary Heart Disease and Relatives of Diabetics. Diabetes, 16:3, 171-174, March 1967.*

In an effort to determine the relationship of "prediabetes" to the development of coronary heart disease, intravenous glucose tolerance was measured in a population of industrial workers who were participating in a prospective study to assess the importance of various factors contributing to the development of coronary heart disease. No significant differences in intravenous glucose tolerance could be detected between groups of control subjects, subjects with a close diabetic relative (parent, sibling or child) or subjects with coronary heart disease (angina pectoris or myocardial infarction). Body surface areas and skinfold thickness were not significantly different among the three groups. Mean serum cholesterol level in the coronary disease group (254 mg. %) was only thirteen mg. % higher than the means of the other two groups which were equal (241 mg. %). There was no significant correlation between glucose tolerance and serum cholesterol. Significant correlation between intravenous glucose tolerance and body fatness was encountered only in the control group.

Lewis, J. P.; Passovoy, M.; Conti, A.; McFate, P. A.; and Trobaugh, F. E., Jr.: The Effect of Cooling Regimens on the Transplantation Potential of Marrow. *Transfusion, 7:1, Jan.-Feb., 1967.*

These experiments were designed to identify those portions of the cooling curve, variations in which most affect the repopulating potential of thawed marrow. Murine bone marrow was suspended in Hanks' solution containing 12% glycerol and 4% calf serum. One ml samples of this suspension were frozen at controlled cooling rates and after thawing the transplantation potential of each sample was bioassayed. The bioassay was based on the colony producing potential of hematopoietic tissue injected into lethally irradiated mice. The cooling curve was divided into five separate phases each of which was studied independently at several levels. At the levels studied, the rate of cooling to freezing, the duration of the pre-freezing plateau and the temperature at which freezing was initiated did not affect the repopulating potential of marrow. However, the repopulating potential of marrow decreased in a linear fashion as: (1) the post-freezing plateau was lengthened or (2) as the rate of cooling from freezing to −100 C was increased.

Lewis, J. P.; Passovoy, M.; and Trobaugh, F. E., Jr.: The Transplantation Efficiency of Marrow Cooled to 100°C at 2°C per Minute. *Cryobiology, 3:1, 1966.*

A technique for freezing and thawing murine bone marrow has been described. The marrow was cooled to −100°C at a rate of 2°C per minute, freezing being initiated at −12°C. After it was thawed, its repopulating potential, as estimated by the hematopoietic colony technique, was 95% of its value prior to freezing. These are the first studies in which this degree of precision in measurement and of efficiency in the preservation of viable mammalian cells has been demonstrated.

Knock, F. E.: Chromosomal Residual Protein-SH Groups in Cancer and Gene Control. *Perspect. Biol. Med., 10:310, Winter, 1967.*

SH-bearing residual protein bound to DNA in chromosomes may play a major role in regulating DNA. Recent work on heterokaryons underscores the necessity for both fine control of genes (as of a single gene or group of genes) and for coarse control mechanisms, with a dominance for "turning on" reactions. The dominance of "turning on" reactions for control systems based on histones appears difficult but less difficult for control systems based also on chromosomal residual protein-SH, where points of modulation by intracellular milieu include especially the chemical signal sent by regulator genes (such as perhaps the

SH-inhibiting Retine) and its chemical target on operator genes, potentially SH-bearing chromosomal residual protein or one of its components. Variable binding of Retine might be expected by intracellular SH compounds of both low and high molecular weight. Availability and concentration of appropriately reactive SH groups on chromosomal residual protein may respond with exquisite sensitivity to a host of intracellular factors such as: oxygen, tension, ph, temperature, hydration, drydogen bonding, and oxidation-reduction potential; and also to levels of SH inhibitors, of metabolites of known regulators like steroids to introduce possibilities of feedback control, and of other effectors, either repressors or inducers or inducers and depressors. In accord with data on heterokaryons, many stimuli capable of generating increased SH-like hypoxia and increased levels of reducing agents, need not be specific. Improved SH inhibitors are needed both to improve clinical cancer chemotherapy and to provide insight into mechanisms of gene control.

Knock, F. E.: Recent Advances in the Treatment of Cancer. *Illinois Med. J., 131:192, Feb. 1967.*

The woman with breast cancer or the man with lung cancer treated only by surgery and radiation therapy has received just those cancer treatments whose failure to improve survival statistics has become clear over the past generation, despite earlier and earlier diagnosis and treatment. For progress, sound local treatment by surgery and radiation must be supplemented by sound generalized treatment for the patient's cancer spread beyond surgical and radiation fields when the patient is first seen. Chemotherapy aimed preferentially at cancer is needed to supplement cancer surgery and radiation, lest rapidly dividing normal cells of wounds and marrow be hit if all rapidly dividing cells are attacked by the chemotherapy. Chemotherapy with selected SH inhibitors has regressed a variety of human cancers without injury to normal wound healing or hematologic status, and with improvement in hematologic status in some patients. Four case histories illustrating such chemotherapy are presented.

The preferential attack by selected SH inhibitors on human cancers and cell division, the apparent universality of an SH inhibitor like Retine as potential cell regulator, the marked susceptibility of SH to most known carcinogens, and the appropriate biologic and chemical characteristics of SH-bearing chromosomal residual protein suggest that residual protein and its SH groups may play a major role in gene control.

Knock, F. E.: Sulfhydryl Inhibitors in Cancer Therapy. *J. Amer. Geriat. Soc., 15:41, Jan. 1967.*

If SH compounds are blocked, cell division fails. SH inhibitors can inhibit cell division of lower forms preferentially, with apparently greater effect on cancer than normal. Use of proper SH inhibitors may open the way to a specific cancer therapy, as shown by data on animal and human cancers. Available data suggest that chromosomal residual protein-SH may regulate DNA directly or indirectly: (1) by reaction with DNA inhibitors like peroxides and Retine; (2) by modifying allosteric effects of regulators like steroids; (3) by becoming an inducer or depressor of DNA through appropriate chemical changes, especially increased availability or concentration of crucial SH groups; or (4) by setting the stage for proper chelation of metal ions.

Derangements in the potentially regulatory SH-bearing residual protein (through DNA mutations or action of adventitious carcinogens) would be expected to produce increased disorder, increased entropy, increased availability of crucial SH, and decreased energy of activation for reaction of such SH groups with active SH inhibitors. Thereby, the susceptibility of human cancers to attack by selected SH inhibitors would be expected to exceed that of normal tissues of origin, a concept in accord with clinical data.

Hass, G. M.; Landerholm, W.; and Hemmens, A.: Inhibition of Intercellular Matrix Synthesis During Ingestion of Inorganic Lead. *Amer. J. Path., 50:815-847, 1967.*

If the hypervitaminosis D regimen was instituted in rabbits ingesting lead subacetate (with or without linseed oil containing the usual lead drier), the customary early tissue changes characteristic of hypervitaminosis D occurred. Later on, however, the vitamin D-induced production of intercellular matrices in arterial intima and in bone did not occur. There was no fibrocellular thickening of the intima of calcified arteries. There was no more than a trace of newly formed basophilic intercellular matrix along the partly resorbed trabecular structure of cancellous bone. However, as soon as the animals were placed on a normal diet, the capacity for vitamin D-induced formation of intercellular matrices was restored. The lead-induced inhibition of matrix production resembled an effect of vitamin C deficiency in some species. The question was raised as to whether many toxic effects due to ingestion of lead and related metallic ions might have a common pathogenesis related to interference in production of intercellular materials among which collagen is perhaps the best-defined.

Deinhardt, F.; Holmes, A. W.; Capps, R. B.; and Popper, H.: Studies on the Transmission of Human Viral Hepatitis to Marmoset Monkeys: I—Transmission of Disease, Serial Passages, and Description of Liver Lesions. *J. Exp. Med., 125:673-688, 1967.*

Inoculation of human serums or plasmas obtained during the early acute phase of viral hepatitis induced chemical and morphological hepatic disease in marmosets in two out of five experimental series. The disease was transmissible in series from marmoset to marmoset with an apparent increased virulence of the causative agent in later marmoset passages. The chemical evidence for the disease was elevation of the activity of SGOT and SICD and of serum bilirubin. In serial liver biopsy specimens interpreted under code, a hepatitis, exhibiting some of the characteristics of human viral hepatitis was readily preceded by the biochemical alterations and persisted after them.

The data reported in these studies indicate that marmosets may be susceptible to human hepatitis. If these observations are confirmed, these animals may provide good experimental models for this disease. Final proof that the hepatitis observed in marmosets is caused by agents of human viral hepatitis is still lacking.

Markowitz, A. S.; Clasen, R.; Nidus, B.; and Ainis, H.: Streptococcal Related Glomerulonephritis: II—Glomerulonephritis in Rhesus Monkeys Immunologically Induced Both Actively and Passively with a Soluble Fraction from Human Glomeruli. *J. Immun., 98:161-170, 1967.*

Glomerulonephritis has been produced in the rhesus monkeys passively by the intravenous injection of sheep antiserum produced against a soluble fraction obtained from pooled human glomeruli (PGT HUGL). This antigen had previously been shown to be chemically similar to and immunologically cross-reactive with a soluble substance from type 12 nephritogenic streptococci.

Glomerulonephritis was also produced in the monkey by active immunization with an alum-precipitate of PGT HUGL as the immunogen.

Immunofluorescence evidence was presented to indicate that the sheep and monkey γ-globulin localized in the glomeruli in the passively produced disease, while autologous γ-globulin was found in the actively induced disease.

No immunofluorescence evidence could be obtained to indicate the presence of the injected material in the glomeruli of the actively immunized animals. The concept is submitted that in this latter group tolerance was broken and that the globulin which localized was antibody-reactive with a determinant grouping on the monkey glomerular basement membrane.

Deinhardt, J. B.; Devine, J.; Passovoy, M.; Pohlman, R.; and Deinhardt, F.: Marmosets as Laboratory Animals: I—Care of Marmosets in the Laboratory, Pathology and Outline of Statistical Evaluation of Data. *Lab. Anim. Care, 17:1, 1-29, 1967.*

The general animal husbandry, the evaluation of biological baseline values and the pathology of wild-caught and laboratory kept marmosets is described.

Anderson, E. T.; Lewis, J. P.; Passovoy, M.; and Trobaugh, F. E., Jr.: Marmosets as Laboratory Animals: II—The Hematology of Laboratory Kept Marmosets. *Lab. Anim. Care, 17:1, 30-40, 1967.*

Studies have been performed on the hematopoietic system of recently captured, laboratory acclimatized marmosets. "Normal ranges" as determined in this study have been compared to the normal ranges in humans and to values found in the rhesus monkey and one other study of marmosets. The similarity of marmoset hematologic values to those of humans lends support to the thesis of using marmosets as laboratory animals suitable for use in human tumor-virus research.

Holmes, A. W.; Passovoy, M.; and Capps, R. B.: Marmosets as Laboratory Animals: III—Blood Chemistry of Laboratory-Kept Marmosets with Particular Attention to Liver Function and Structure. *Lab. Anim. Care, 17:1, 41-47, 1967.*

Blood chemical constituents and liver function tests were determined in a number of wild-caught, laboratory adapted marmosets. With few exceptions, marmoset values varied little from values observed in normal humans. The histological structure of marmoset liver as examined by light microscopy did not differ greatly from that of human liver.

Wiener, A. S.; Moor-Jankowski, J.; and Gordon, Eve B.: Marmosets as Laboratory Animals: V-Blood Groups of Marmosets. *Lab. Anim. Care, 17:1, 71-76, 1967.*

Thirty-one marmosets from the Department of Microbiology, Presbyterian-St. Luke's Hospital, Chicago, have been tested for A, B, H and Lewis blood factors. All the animals tested had A group substance in the saliva, but no B or Lewis substance. H substances appeared to be present but seemed very poorly developed compared to human secretor saliva, so that little or no inhibition of anti-H lectin occurred except when the reagent was highly diluted. The red cells lack A and H blood factors, but there is evidence that they have a B-like agglutinogen.

Marmoset sera generally contain no or only weak heteroagglutinins for human red cells, regularly lack anti-A and generally also lack anti-B. Some marmoset sera, however, contain active anti-B, which is a further evidence that the B-like property of their red cells is not identical with the B agglutinogen of human red cells. The saliva of all 31 marmosets lacked the Lewis substance. Red cells of two marmosets tested proved to contain the I factor.

The presence in human serum of potent hetero-agglutinins for marmoset red cells rendered such reagents unsuitable for testing marmoset red cells. For this reason, tests for Rh-Hr factors were inconclusive. Tests with lectins confirmed the absence from marmoset red cells of factors H, A_1 and N^V.

Deinhardt, F.; Holmes, A. W.; Devine, J.; and Deinhardt, J.: Marmosets as Laboratory Animals: IV—The Microbiology of Laboratory Kept Marmosets. *Lab. Anim. Care, 17:1, 48-70, 1967.*

The poor condition of marmosets on arrival into the laboratory and their potential disease hazards for man appear on first examination to negate some of their value as laboratory animals. But their disadvantages in these respects are not greater than other nonhuman primates and marmosets adapted to the laboratory life offer several advantages. They appear to be both free of circulating antibodies and susceptible to most of the common

human viruses and so would be a good choice of animal for study of experimental infections. They may have a particular usefulness in the study of human viral hepatitis and tissue cultures prepared from marmoset kidneys are susceptible to a large number of human viruses.

McCreary, P. A.; Battifora, H.; Hahneman, B.; Laing, G. H.; and Hass, G. M.: Leukocytosis, Bone Marrow Hyperplasia and Leukemia in Chronic Magnesium Deficiency in the Rat. *Blood, 29:683-690, 1967.*

Hematologic studies, including bone marrow examinations, have been done on a series of rats which were on a magnesium-deficient diet, with or without 2-AAF supplementation. Leukocytosis and granulocytosis could be maintained in these deficient rats by decreasing their intake of magnesium and could be reversed by the addition of magnesium. The bone marrows of the magnesium-deficient group showed granulocytic hyperplasia; the bone marrows of the deficient 2-AAF supplemented rats showed erythrocytic hyperplasia, as well as granulocytic hyperplasia. Chronic granulocytic leukemia developed in two magnesium deficient rats and persisted after magnesium supplements were given. This leukemia has been successfully transplanted into newborn rats.

Harrison, W. H. and Whisler, W. W.: Detection and Study of a Cyclization Step Preceding the Formation of a Fluorescent Product in Tyrosinase-Catalyzed Adrenaline Oxidation. *Arch. Biochem., 114, 108-114, 1965.*

The fluorescent oxidation product formed in the tyrosinase-catalyzed oxidation of adrenaline has been shown, by a tritium tracer technique, to be formed via an intermediate cyclization step. This step was found to have the same time course relationship in respect to the fluorescent product formation as does the initial oxidation to the uncyclized *o*-quinone. Pertinent features of the mechanism were revealed by the action of catechol, dopamine, and related compounds on the system. Of significance was an activation effect of catechol and dopamine on the cyclization step and an inhibition effect of catechol on the fluorescence formation step. The latter effects were found to be due to the functioning of an electron carrier system produced from catechol or dopamine at an early stage of the reaction. A mechanism consistent with the results is presented.

Harrison. W. H.;Whisler, W. W.; and Ko, S.: Detection and Study by Fluorescence Spectrometry of Stereospecificity in Mushroom Tyrosinase-catalyzed Oxidations. *J. Biol. Chem., 242:7, 1660-1667, April 1967.*

Stereospecific reactions were detected in a fluorescence spectrometric examination of the catalytic oxidation of the optical isomers of adrenaline, noradrenaline, and 3,4-dihydroxyphenylalanine (dopa) by mushroom tyrosinase. The stereospecificity, which is preferential rather than absolute, can be detected by following either an initial step of the oxidative sequence or a later fluorescence formation step. Compared with catechol and 2-(3′, 4′-dihydroxyphenyl)ethylamine (dopamine) on the basis of the initial oxidation step, the velocities of their oxidation decrease in the following order: catechol > L(−)-dopa > dopamine > D(+)-dopa > L(+)-adrenaline > D(−)-adrenaline > L(+)-noradrenaline > D(−)-noradrenaline. The velocities of formation of fluorescent intermediates produced from adrenaline and noradrenaline decrease in the following order: L(+)-adrenaline > D(—)-adrenaline > L(+)-noradrenaline > D(−)-noradrenaline. L(—)-Dopa was shown to have a more pronounced effect than D(+)-dopa as an activator both of the tyrosinase-catalyzed oxidative cyclization of adrenaline and of the fluorescence formation step. Approximate steady state oxygen Michaelis constants K_m (O_2), ascertained during the oxidation of the optical isomers of adrenaline, were found to be different for each isomer, the K_m (O_2) for the D(−) isomer being almost 2 times higher than that for the L(+) isomer. The observed effects of the side chain substituents on the oxidation velocities suggest that tyrosinase contains a stereospecific reaction rate control site. It is proposed that the side chains bind to the control site through chelation with copper and function as reaction rate modulators.

Schneir, M. L. and Rafelson, M. E., Jr.: Isolation and Characterization of Two Structural Isomers and N-Acetylneuraminyllactose from Bovine Colostrum. *Biochem. Biosphys. Acta., 130, 1-11, 1966.*

A method has been described for the isolation of two structural isomers of *N*-acetylneuraminyllactose from bovine colostrum. The two isomers were shown to be *N*-acetylneuraminyl-(2→3)-β-D-galactopyranosyl-(1→4)-D-glucopyranose and *N*-acetylneuraminyl-(2→6)-β-D-galactopyranosyl-(1→4)-D-glucopyranose. The latter isomer had not previously been reported to occur in bovine milk or colostrum. Although both isomers were cleaved completely by the purified neuraminidase (EC 3.2.1.18) from influenza virus, the isomers differed in their pH optimum, K_m and *V*. The mode of linkage of *N*-acetylneuraminic acid to lactose appears to influence both the rate of formation and breakdown of the enzyme-substrate complex.

Gerbeck, C. M., Bezkorovainy, and Rafelson, M. E., Jr.: Glycopeptides Obtained from Human Haptoglobin 2-1 and 2-2. *Biochemistry, 6:403-411, 1967.*

Two major types of glycopeptides differing in amino acid composition were isolated from type 2-1 human haptoglobin. One type contained large amounts of aspartic acid, alanine, and threonine with aspartic and glutamic acids as the NH_2-terminal residues. The other type contained mainly aspartic acid and histidine, both of which were found as the NH_2-terminal groups. Both types of glycopeptides had essentially the same carbohydrate composition: 5-6 moles of hexose (galactose and mannose), 3-4 moles of *N*-acetylglucosamine, and 0-3 moles of *N*-acetylneuraminic acid, with fucose present in some units but absent in others. Molecular weights of the glycopeptides were in the range of 2000-3000, variations being probably due to the length of the peptide chain and/or to the number of *N*-acetylneuraminic acid and fucose residues.

On the basis of the size and composition of the glycopeptides isolated from the native haptoglobin of type 2-1, it is estimated that the intact molecule (mol wt 200,000) contains approximately 13 such units. The carbohydrate and amino acid composition of some haptoglobin 2-2 glycopeptides was essentially identical with that of the corresponding haptoglobin 2-1 glycopeptides, suggesting the presence of approximately 26 oligosaccharide residues/molecule (mol wt 400,000).

Kornel, L.; Starnes, W. R.; and Hill, A.: Quantitative Paper Chromatography of Urinary Corticosteroids in Essential Hypertension. *Fed. Proc., 26:2, March-April 1967.*

The results of our previous studies on metabolism of corticosteroids in essential hypertension pointed to an increased production of 17-hydroxycorticosteroid sulfates in patients with essential hypertension (J. Clin. Endocr. *23*:904, 1965). To further elucidate this finding, individual C_{21} α-ketolic urinary steroids have been separated and estimated by quantitative paper chromatography in ten normotensive subjects and ten patients with uncomplicated essential hypertension. The methods used were essentially those described by us previously (Anal. Biochem. *6*:82, 1963), modified so as to separately determine paper chromatographic pattern of steroids in the free, glucuronide, and sulfate fractions (Biochemistry *4*:444, 1965). The results obtained revealed that the hypertensive patient had statistically significantly higher ($P<0.02$) urinary excretion of: (1) *sulfate* conjugated *polar* corticosteroids not reduced in ring A, and (2) *free* metabolites not reduced in ring A. These findings suggest that patients with essential hypertension have a decreased ability to reduce ring A of steroid nucleus, and that they produce more metabolites not requiring ring A reduction, particularly 6-hydroxycortisol sulfates. These compounds may have a direct bearing on the etiology of essential hypertension.

Kornel, L. and Takeda, R.: Studies on Steroid Conjugates: V-Urinary 17-Hydroxycorticosteroids in Essential Hypertension. *J. Clin. Endocr., 17:233, 1967.*

Urinary excretion of free, glucuronide and sulfate conjugated 17-hydroxycorticosteroids (17-OHCS) was estimated in 20 normotensive subjects and 20 patients with uncomplicated essential hypertension; in each of these 17-OHCS fractions, less polar (methylene chloride-extractable) and more polar (ethyl acetate-extractable) steroids were determined separately (in the conjugated fractions, following β-glucuronidase hydrolysis and solvolysis, respectively). In addition, excretion of "total" conjugated 17-OHCS was measured by 2 different methods: 1) estimating all the conjugates, and 2) estimating all but very polar conjugates (*e.g.*, 6α-hydroxycortisol-21-sulfate, tetrahydrocortisol-3,21-disulfate). The results obtained showed the following statistically significant differences between the 2 groups of investigated subjects: 1) excretion of 17-OHCS glucuronides was lower in hypertensive patients; 2) excretion of 17-OHCS sulfates was higher in these patients; 3) the higher excretion of sulfates in hypertensives was mainly due to an increase in the more polar steroids in this fraction; 4) the lower excretion of glucuronides was due only to a decrease in the less polar steroids in the glucuronide fraction; 5) the ratio of total glucuronide to total sulfate conjugated 17-OHCS was markedly decreased in hypertensives; 6) the ratio of total free steroids to total sulfate conjugates was also decreased in hypertensives; 7) the ratio of more polar to less polar steroids in the sulfate fraction was markedly increased in hypertensives. There was no statistically significant difference between normotensives and hypertensives in the sums of the urinary excretion of sulfates and glucuronides, nor in the excretion of total conjugated 17-OHCS measured by the technique extracting and estimating all conjugates. However, there was a highly significant difference in the excretion of that fraction of conjugated 17-OHCS which is measured by the latter method, but not by the method not estimating very polar steroid sulfates, this fraction being markedly increased in hypertensives. The results of this study closely correlate with those of an analogous study in plasma, thus pointing to an altered metabolism of corticosteroids in patients with essential hypertension. The increased production of polar conjugated 17-OHCS sulfates, deduced from these studies, may be of primary importance in the etiology of this disease.

ESBYTERIAN-ST. LUKE'S HOSPITAL MEDICAL BULLETIN